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NORTH AMERICA

Neurologic Disturbances

Volume 47—Number 6

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THE MEDICAL CLINICS

OF NORTH AMERICA

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THE MEDICAL CLINICS
OF NORTH AMERICA

Nationwide Number

Neurologic Disturbances

FRANCIS M. FORSTER, M.D.
Guest Editor

THREE-YEAR CUMULATIVE INDEX
(1961, 1962 and 1963)

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Difficult Diagnostic Problems

May, 1963—*from New York*

The Liver and Its Diseases

July, 1963—*from Philadelphia*

Diseases of the Kidney

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Recipients Named for W. B. Saunders Company Writing Fellowship Award

To MARK its 75th Anniversary in 1963, the W. B. Saunders Company late last year announced that it was making available $15,000 for an unusual writing award. Its purpose was to provide financially for a year's leave of absence for an investigator who had been doing fruitful and significant biomedical laboratory research over the past several years, and who would like to have time for preparation of his work in monograph form.

So many outstanding applications were received by the Selection Board from medical scientists of distinguished accomplishment that an Executive Committee consisting of Robert F. Loeb, Rene J. Dubos, Henry Allen Moe and Robert S. Morison recommended to the Saunders Company that it mark its anniversary not with one, but with two equal fellowships, each in the full amount of the original offer.

The Saunders Company accepted this recommendation and is pleased to announce that the two recipients chosen by the eminent selection board are Dr. Herman M. Kalckar, of Harvard Medical School, and Dr. Paul B. Beeson, of Yale University School of Medicine.

Dr. Kalckar will be writing on Biological Patterns of Cells in Developmental Defects and Disease States.

Dr. Beeson will be writing on Associations of Specific Infections with Certain Disease States of Man.

Formal presentation of the awards will be made individually to each grantee at two dinners to be held in the fall and early winter.

Symposium on Neurologic Disturbances

FOREWORD

FRANCIS M. FORSTER, M.D.

MEDICINE of the twentieth century is in a period of great growth and development. This reflects the orientation of the modern physician, the financial support for research, and the growth and development of the universities. Neurology is in the forefront in this period of growth and development, for the neurologist by tradition is oriented in basic sciences as well as in clinical disciplines. Therefore, almost the entire personnel in the field of neurology has a personal interest in seeking out new knowledge. Private foundations and governmental agencies, particularly the National Institute of Nervous Diseases and Blindness, have done much to sponsor research. So it is timely that clinically applicable fruits of some of these researches be laid before the readers of this publication.

We have tried to place before you in some depth the most important entities in the neurologic field, such as epilepsy, parkinsonism, multiple sclerosis, vascular disease and trauma. The central nervous system manifestations of metabolic disorders are particularly important. Myasthenia is a relatively uncommon disease and the myopathies described by Doctor Shy are uncommon, but the scientific approach to the diagnosis of muscle disorders and the management of myasthenia are timely. Often the neurological examination is thought to be a simple bedside examination, but, as in all clinical examinations, there is a need for supporting, quantitated testing, as Doctor Thompson and Doctor Kløve emphasize. The status of chemotherapy in brain tumors is not yet ideal, but it is necessary to review it and know where we stand. Our confreres in the discipline of psychiatry have become more engrossed with the structure and function of the nervous system in recent years; the excellent paper by Doctor Finley presents the nervous system structure for behavioral manifestations. Neurochemistry is a rapidly expanding field, and it is to be hoped that the cause and eventual prevention or cure of multiple sclerosis will arise from studies in this area.

I am grateful to the W. B. Saunders Company for the privilege and honor of serving as Guest Editor, and I wish to express my warmest thanks to my colleagues who have expended so generously their time and talents on the preparation of the articles that follow.

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Neurologic Manifestations in Diabetes Mellitus

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Diabetes mellitus is a disorder of carbohydrate metabolism, the underlying metabolic mechanisms of which are not well understood.[7] The end result of the biochemical defects in diabetes mellitus is hyperglycemia, which appears to be associated with both peripheral underutilization and overproduction of glucose. Although the basic defect in the diabetic patient is in the carbohydrate metabolism, there are also disturbances of fat and protein metabolism, including defects of fatty acid synthesis, protein synthesis and a few others.

The nervous system is frequently involved in diabetes mellitus.[3, 10, 12] The manifestations appear to be related both to the underlying metabolic defects and to the vascular changes, not to mention complications arising from insulin-induced hypoglycemia.[1]

Nervous system manifestations of diabetes can be classified as follows:

A. Peripheral nervous system syndromes (diabetic neuropathies)
    1. Symmetric peripheral neuropathy (diabetic polyneuropathy)
    2. Asymmetric neuropathy (mononeuropathy, mononeuropathy multiplex)
    3. Radiculopathy
    4. Autonomic visceral neuropathy
    5. Cranial neuropathy and retinopathy
B. Spinal cord syndromes
    1. Diabetic myelopathy, diabetic pseudotabes
    2. Diabetic amyotrophy
    3. Acute vascular syndromes; myelomalacia

- C. Cerebral syndromes
  - 1. Cerebrovascular accidents and chronic cerebrovascular disease
  - 2. Diabetic coma
- D. Neurologic abnormalities in infants of diabetic mothers

PERIPHERAL NERVOUS SYSTEM SYNDROMES (DIABETIC NEUROPATHIES)

The incidence of diabetic neuropathy is hard to ascertain from the literature because of the different criteria used in establishing the diagnosis of neuropathy. If one accepts decreased reflexes with no other symptoms or signs, the incidence can be estimated at almost 90 per cent. When more strict criteria are used, frequencies ranging from 25 to 50 per cent are found.[2, 12]

The basic cause and pathogenesis of diabetic neuropathy are far from clear and appear to lie between ischemia of the nerves from occlusive vascular disease and damage due to toxic-metabolic factors. There is no uniform agreement as to which of these two mechanisms plays the primary role or whether the two are interrelated. Metabolic factors proposed include vitamin B deficiencies, hyperglycemia, abnormalities in the enzyme system and presence of toxic metabolites in the course of carbohydrate turnover. Recently specific angiopathy, other than arteriosclerosis, has been reported in the vasa nervorum of diabetics with neuropathy consisting of luminal constriction and thick vascular walls with accumulation of mucopolysaccharides and other glycoproteins.[6] Such changes appear to correlate well with similar changes found in renal glomeruli and other capillaries in the diabetic patient. Recognition today of such specific small vessel disease in diabetes mellitus, probably related to disturbance in mucopolysaccharide metabolism, gives additional support to the theory that diabetes is not solely a disease of deficient insulin activity. Although neuropathy is more common among patients with poorly controlled diabetes, there is by no means a definite correlation between neuropathy and diabetic control.

The pathologic change of the nerves consists of diminution in the number of nerve fibers with patchy demyelination followed by axis cylinder degeneration and proliferation of the endoneural and perineural connective tissue.[3, 15] Ischemia from arteriosclerosis or specific vascular disease of the vasa nervorum, described previously, could be responsible for such changes.

Symmetric Peripheral Neuropathy (Diabetic Polyneuropathy)

This type of neuropathy is most commonly seen among diabetics during the fifth and sixth decades of life. The onset is insidious and is characterized primarily by sensory manifestations which are usually more pronounced in the lower extremities. Burning paresthesias aggravated by heat, pain and tenderness of varying degree in the distal part of legs, especially the feet, usually precede any objective sensory loss, which is usually of a glove-stocking distribution. The latter may be virtually absent even with the most distressing diabetic causalgias. The pain is often shooting and may simulate the lightning pains of tabes dorsalis. Sometimes one sees repeated relapsing episodes of such painful conditions lasting for several weeks or months. Early in the course of this neuropathy there is a loss of vibration sense and diminution of deep tendon reflexes. Impotence as part of the neuropathy may be seen in as many as 50 per cent of the cases. Motor paralysis which is chiefly distal in distribution, trophic ulcers and loss of bladder sphincter control due to degeneration of pudendal nerves are seen in protracted cases. In such cases, associated visceral neuritis or spinal cord involvement may be apparent.

If the neuropathy develops early in the course of diabetes, it may remain as a painful syndrome and will subside under good diabetic control: As part of a severe long-standing and usually poorly controlled diabetes, the neuropathy presents with true deficit and the prognosis of recovery is less favorable.

An unusual form of chronic progressive neuritis is associated with anesthesia of the feet and painless ulcers in the absence of any other striking change.

In general, diabetic polyneuropathy may progress or remain stationary for a long time but usually responds to control of the diabetes, vitamin B therapy, rest and mild physiotherapy. Thiamine HCl, nicotinic acid and vitamin C, 100 to 200 mg. each daily, are recommended. Vitamin B_{12} 1,000 micrograms intramuscularly daily is especially useful in painful neuropathies. Peripheral vasodilators, such as papaverine 180 mg. (3 grains) daily or Arlidin 8 mg. three times a day are important parts of the therapy.

Asymmetric Neuropathy (Mononeuropathy and Mononeuropathy Multiplex)

This type in its clear form occurs less frequently, although cases with associated peripheral neuropathy of the type just described are more common.[12, 14] It is often seen in early diabetes or in the prediabetic state, and the onset is usually rapid. Pain is usually early, and paralysis and atrophy follow the distribution of a specific nerve or nerves. Radicular involvement is commonly seen in such cases. Peroneal, femoral, ulnar and median nerves are most commonly affected. It appears that peripheral nerves are injured at some local vulnerable site as they pass over bony prominences or through ligamentous and bony tunnels. Typical tardy ulnar palsy and carpal tunnel syndromes can occur alone or as part of mononeuritis multiplex.[12]

The prognosis in these cases is usually better than that in symmetric peripheral neuropathy. The treatment is the same.

Radiculopathy

Root involvement may be manifested by pain in the proximal body segments, often difficult to localize. Multiple roots and plexuses may be involved alone or as part of mononeuritis multiplex, giving rise to asymmetric proximal and distal pain and variable patterns of weakness.[14] Herpes zoster may be associated with radiculitis in some of the cases. A picture simulating Guillain-Barré syndrome may occasionally be seen associated with bilateral proximal weakness, pain, muscle tenderness, peripheral sensory loss and sometimes loss of sphincter control.

Autonomic Visceral Neuropathy

Such a neuropathy is usually seen with diabetes which has lasted for a number of years and may appear alone or may accompany ordinary diabetic neuropathy. Symptoms include intermittent nocturnal diarrhea, incontinence, delayed emptying of the stomach, orthostatic hypotension, tachycardia, peripheral vasomotor changes, etc. Trophic changes in the joints may result in Charcot arthropathy and is usually found in the ankle.

Cranial Neuropathy and Retinopathy

Cranial neuropathy occurs less frequently and often is seen in long-standing diabetes. It most commonly presents with paresis of the oculomotor, facial and auditory nerves and pupillary abnormalities.[5, 11, 13] The latter include irregularities of pupils as to size and shape, abnormal reactions and often simulate Argyll Robertson pupils.

The onset is usually sudden and probably represents acute ischemic neuropathy from occlusion of small nutrient nerve vessels.

Visual failure in diabetes mellitus is usually due to retinal involvement and cataracts. Optic neuritis is only rarely seen. Primary optic atrophy probably does not occur, although recently bilateral optic atrophy and diabetes have been reported to occur in several members of families, sometimes associated with bilateral nerve deafness.

Ocular palsies may involve any of the oculomotor nerves and may be unilateral or bilateral, symmetric or asymmetric, involving one or more muscles. Unilateral 6th or 3rd nerve palsies are probably most common, followed by bilateral 6th and 3rd. In most cases the pupils are spared, and this can be used as a differential point when diagnosis of an intracranial aneurysm is contemplated. Pain often accompanies these palsies which may be retro-orbital or may involve the ipsilateral side of the face. Recovery from the palsies is usually within two or three months. Recurrent ocular palsies are not infrequent, as are also recurrent palsies of other cranial nerves mentioned above.[13]

Retinopathy occurs in two-thirds of patients with long-standing diabetes and accounts for a wide variation of funduscopic abnormalities.[8] The classical features of retinopathy are small irregular hemorrhages, dilated and tortuous retinal veins and hard, round, white exudates usually some distance from the vessels. There is no relationship between the severity of diabetes and the degree of retinopathy. A sharp decrease of visual acuity is usually the result of macular involvement. In 1944, Ballantyne called attention to microaneurysms as the earliest lesions in diabetic retinopathy. These are found in the perimacular area and are present as circular or oval projecting nodules.

SPINAL CORD SYNDROMES

Diabetic Myelopathy and Diabetic Pseudotabes

Clinical syndromes simulating tabes dorsalis may occur in diabetes. Deep tendon reflexes are absent in the legs. There are proprioceptive ataxia and pains, often lightning in character. Argyll Robertson pupils and Charcot joints add to the possibility of confusion with syphilis. The posterior column degeneration found in these cases is at least partially secondary to retrograde degeneration from spinal ganglia and dorsal roots. In some cases, the picture may resemble that of combined system disease from dorsal lateral degeneration of the cord, and occasionally in severe cases the signs may suggest transverse myelopathy.

Diabetic Amyotrophy

Flaccid motor weakness and atrophy more severe in the proximal muscle groups may take a chronic form and often simulate progressive muscular atrophy. Pain is not uncommon in such cases.[9] Pathologically, one finds a loss of anterior horn cells which are for the most part retrograde from involvement of motor roots and nerves. The condition is usually reversible with achievement of good diabetic control and physiotherapy.

Acute Vascular Syndromes; Myelomalacia

This is the result of vascular occlusion, ischemia or, less commonly, hemorrhage secondary to an accelerated arteriosclerotic process. Such insults may cause extensive myelomalacia and paraplegia if the anterior spinal artery is occluded. No specific angiopathy has been described in the spinal cord.

CEREBRAL SYNDROMES

Acute focal cerebral manifestations of diabetes mellitus are invariably on the basis of degenerative vascular disease. No specific angiopathy has been described as yet in the brain. Diffuse syndromes associated with coma are the result of ketoacidosis.

Cerebrovascular Accidents and Chronic Cerebrovascular Disease

Acute stroke syndromes secondary to ischemia, thrombosis and hemorrhage are the result of arteriosclerotic vascular disease accelerated by the diabetic process. Uremia and hypertension induced by an associated Kimmelstiel-Wilson syndrome are additional contributing factors. Cerebral infarction occurs one and one half times more frequently in diabetic patients as compared to nondiabetics; cerebral hemorrhage is only slightly more common in nondiabetic persons.

Fusiform enlargement and tortuosity of the basilar artery is not uncommon and may produce brain stem syndromes with intermittent insufficiency or deficit from direct pressure effect upon cranial nerves and brain stem structures. If the internal carotid system is involved, hemiplegias, homonymous hemianopsias, aphasias and hemihypalgesias are encountered.

Chronic cerebrovascular disease with mental deterioration and variable focal signs are due to widespread arteriosclerotic process. Repeated insulin hypoglycemic episodes may be responsible in some cases.

Diabetic Coma

Coma from ketoacidosis is the most serious complication in the course of diabetes mellitus. It is due to an increase in fat catabolism and accumulation of ketone bodies far in excess of what the body can handle. Associated dehydration with subsequent reduction of blood volume, circulatory collapse, renal failure and electrolyte imbalance are added complicating factors. Among electrolyte disturbances the most serious is sodium loss due to the osmotic activity of glucose in the renal tubules and the excess excretion in the urine of keto acids as sodium salts. Loss of sodium from vomiting is also a contributing factor. Potassium loss may also become serious from inadequate intake, loss of gastrointestinal fluid and increased urinary excretion. The serum levels of either sodium or potassium may be misleading, for they may be normal or even elevated in the face of serious body depletion of these electrolytes.

Important precipitating factors of diabetic coma are infections, surgery, gastrointestinal disturbance, alcohol excess and omission of insulin.

Specific pathologic changes in the brain due to acidosis are not found.

Prodromal symptoms include increasing weakness, thirst, dull headache, abdominal and muscle pain, nausea, vomiting, drowsiness and hyperpnea. As the patient lapses into stupor and coma there is apparent deep breathing (Kussmaul respiration), rapid and feeble pulse, flushed face, dry skin and mucous membranes, and characteristic "fruity" odor of acetone on the breath. Hypotension, anuria and circulatory collapse may occur later.

The diagnosis presents a problem in that it must be differentiated from other comas, especially hypoglycemic. In the latter the onset is rapid, the respirations are normal, the patient is sweaty, and muscular twitchings and positive Babinski sign are present.

Although physical findings are useful in the diagnosis, the essential diagnostic test is the finding of hyperglycemia with values sometimes of 2,000 mg. or more and a decrease of blood pH. Although not as accurate, determination of carbon dioxide combining power is a useful diagnostic test; values below 25 volumes per hundred occur in the case of deep coma.

Treatment is directed toward correcting the precipitating factors, restoration of salt and water loss by the administration of sodium chloride and glucose solutions, and correction of carbohydrate utilization, ketosis and acidosis by the administration of insulin and in severe cases sodium bicarbonate. In presence of significant renal insufficiency one should be careful with the administration of water, for water intoxication may be precipitated with resulting convulsions.

In the course of treatment, as the patient recovers consciousness, there may be marked flaccid paralysis due to hypopotassemia from continued loss of potassium in the urine and a shift of potassium in the cells. Administration of potassium two or three hours after initiation of therapy will prevent such an occurrence.

NEUROLOGIC ABNORMALITIES IN INFANTS OF DIABETIC MOTHERS

Children of diabetic mothers have a high mortality rate and a greater chance of malformation than normal children. The incidence of such malformations, in various reports reviewed by Dekaban, was estimated at from 3.6 to 15 per cent or more. This is compared to 0.5 to 1 per cent of congenital malformations in normal controls.[4]

The neurologic congenital defects have included hydrocephalus, anencephaly, malformations of the spine, meningocele, deafness, intracranial hemorrhage, cerebral diplegia and mental deficiency.[4] Causative factors capable of acting as noxious agents disturbing normal development of the fetus in a diabetic mother are for the most part related to a poor control of the diabetic state. Ketoacidosis, hypoglycemia and hormonal imbalance are important factors. Ketone bodies can pass the placenta and interfere with cerebral respiration of the fetus. Hypoglycemia has been shown to produce injury to the developing neural elements, with resulting malformation. Less is known regarding hormonal abnormalities; however, birth of oversized babies to diabetic mothers suggests an imbalance of the growth hormone. Regularly occurring morphologic cellular changes in the hypothalamic nuclei of diabetic patients is probably of importance in this regard.

SUMMARY

The nervous system is commonly involved in the course of diabetes mellitus.

The peripheral nervous system is more vulnerable to damage and the presenting pictures include a symmetric peripheral neuropathy, mononeuropathy or mononeuropathy multiplex, radiculopathy, autonomic and cranial neuropathies.

The spinal cord is infrequently involved. Most common pictures are those of diabetic pseudotabes, combined system disease and diabetic amyotrophy.

The brain is the site of acute vascular insults due to an accelerated atherosclerotic process. Diabetic coma, the most serious complication in diabetes, is due to accumulation of ketone bodies far in excess of what the body can handle.

Children of diabetic mothers have a high mortality rate and high incidence of cerebrospinal congenital malformations.

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Neurologic Manifestations in Liver Disease

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NEUROLOGIC and psychiatric manifestations in hepatic failure have been extensively reviewed ever since the important contribution of Frerichs in 1860 on hepatic coma. A variety of symptoms has been described, ranging from simple personality change, episodic neurologic and mental deficit to chronic dementia, acute encephalopathy and coma.[1, 4, 6, 11] It is estimated that about one third of all patients with hepatic cirrhosis may die in coma. The central nervous system is usually diffusely involved, and the onset of the neurologic symptoms may be acute or chronic. The course may take a progressive or episodic pattern.

ETIOLOGY AND PATHOGENESIS

In spite of extensive experimental work, the etiology and pathogenesis of neurologic manifestations in hepatic disease remain problematic.[5, 6, 13] The possibility of a specific neurotoxic agent, probably of nitrogenous origin, liberated into the blood stream because of liver damage has been entertained ever since the original observation by Hahn in 1893 on meat intoxication in dogs with Eck fistula. Such a toxic substance was held responsible for an intracellular metabolic abnormality in the brain, giving origin to reduced cerebral oxidation.

Although a number of toxic substances have been proposed, no single factor has as yet been a satisfactory explanation in all cases. Of the voluminous work accumulated over the years on the biochemistry of hepatic encephalopathy, most emphasis has been placed on the role of ammonia and amino acid products. These substances are found elevated in hepatic coma and at times in liver disease without neurologic deficit.[5, 6] They are absorbed from the gut and normally are detoxified by the liver. In hepatic disease they may reach the systemic circulation by escaping through the damaged liver parenchyma or through the portal collateral channels and may cause cerebral disturbances.[11] In addition, nitrogenous substances, derived from proteolysis and poor deamination in the damaged liver, may act as toxic agents.[12]

Although the increase in blood ammonia in liver disease has been incriminated by many authors as the responsible factor for the cerebral manifestations, there has been considerable dispute as to its over-all etiologic significance. The disagreement stems from the fact that there is no constant relationship between the severity of the hepatic or neurologic disorder and the level of ammonia.[10] Moreover, therapeutic measures directed toward the correction of hyperammonemia are often either unsuccessful or at best transiently effective in alleviating the neurologic deficit.[5, 10] Such discrepancies, however, are subject to a number of explanations. One factor is probably related to the impaired uptake, storage and detoxification of ammonia by the peripheral tissues in liver damage. This will allow for rapid return of abnormal ammonia levels even when large amounts of this substance are removed from the blood. Another factor is the variable permeability of ammonia through the blood-brain barrier depending upon blood pH. This will allow for the greater toxic effect of ammonia in cases of complicating alkalosis, which is not uncommon in liver failure. It is generally stated that the ammonia theory for liver encephalopathy fits best in the cases of hepatic disease with portal caval shunts. In such cases, considerable ammonia can be released into the systemic circulation in the presence of large amounts of nitrogenous substances in the gut.[5, 6] It is in these situations that good correlation exists between blood ammonia levels, uptake of ammonia by the brain and the severity of cerebral disturbance. Moreover, these are the cases responding the best to measures reducing blood ammonia.

The mechanism by which the circulating ammonia produces cerebral symptoms is not clear. A provocative theory is that of Bessman,[2] who, in an attempt to explain the decreased oxygen consumption and hence cerebral symptoms in liver failure, advanced the following theory. In the process of ammonia detoxification by the brain, ammonia depletes a-ketoglutarate by combining with it to form glutamic acid. Depletion of a-ketoglutarate slows down carbohydrate metabolism and oxidative phosphorylation in the brain. This in turn impairs cerebral function with resulting clinical deficit. This theory has not been uniformly accepted. Another concept discussed by Dastur[6] is that the excess cerebral ammonia converts glutamic acid to glutamine and thus depletes the stores of ATP, which is necessary for this conversion. Depletion of ATP will impair synthesis of acetylcholine, which is important for normal brain function. This hypothesis also does not seem adequate, since less than 1 per cent of metabolically derived energy is utilized for acetylcholine metabolism. A third theory, advanced by Weil-Malherbe, implicates direct toxic effect of the ammonium ion at the enzymatic level by disturbing normal ionic flux across neural membranes or by interference with synaptic transmission. It is apparent from this discussion that the problem is far from clear and needs more study.

A few words should be said about the role of amino acids and other possible compounds in the production of hepatic encephalopathy. The presumed toxicity of amino acids, which are found elevated in the blood of patients with liver coma, is thought to be tied up with ammonia production. However, it may be due to a disturbance of cerebral metabolism arising from imbalance of tissue amino acids or accumulation of carbon side chains with toxic properties. Some specific amino acids and amino acid products which have been implicated in the production of coma include methione and indoles derived from tryptophan. The former was found increased in patients with chronic hepatic disease. Its oral administration can produce neurologic deterioration with hyperammonemia preventable by nonabsorbable antibiotics. Indoles, known to be toxic to brain slices, are produced in the gastrointestinal tract from tryptophan and are normally detoxified in the liver. Such substances were held responsible for the neurologic symptoms by escape into the general circulation.

The implication of serotonin in the pathogenesis of hepatic coma was based upon the observation that administration of 5-hydroxytryptophan (serotonin precursor) improves the electroencephalographic abnormality in hepatic failure. This led to the hypothesis of a serotonin deficiency in the brain from the inability of the liver to convert tryptophan to 5-hydroxytryptophan. However, no clinical improvement resulted from infusion of 5-hydroxytryptophan.

Electrolyte disturbances commonly seen in hepatic failure, often capable of producing profound changes in the state of the sensorium, are secondary phenomena and not primary etiologic factors in hepatic encephalopathy. Hyponatremia, hypokalemia and hypomagnesemia are the most important electrolyte abnormalities encountered.[14]

PATHOLOGY

Neuropathologic changes in liver disease have been described in great detail.[1, 4] They are mostly found in areas with dense neuron population, including the cerebral cortex, basal ganglia, thalamus, brain stem and cerebellum. Gross changes may sometimes include cavitation and atrophy of the basal ganglia and cerebral cortex. Although acute and chronic neurologic changes may be severe, especially in the cortex and basal ganglia, the most characteristic changes include an increase in the size and number of protoplasmic astrocytes with large vesicular nuclei and prominent nuclear membranes. However, the presence of such changes is neither constant nor limited to liver disease. In addition to the cellular change, demyelination may occur and can be diffuse, patchy or perivascular, and most prominent in the deeper cortical layers and the adjacent white matter. Mild degeneration may be seen in the spinal cord involving primarily the lateral and in some cases the posterior columns.

CLINICAL ASPECTS OF HEPATIC NEUROLOGIC DISEASE

Classifications proposed for the neurologic complications of liver disease usually divide the picture into acute, chronic and recurrent encephalopathy or encephalomyelopathy. Our classification will deal separately with the myelopathies: (1) acute hepatic encephalopathy and coma (2) episodic hepatic encephalopathy (3) chronic hepatic encephalopathy (4) hepatic myelopathy or encephalomyelopathy.

Acute Hepatic Encephalopathy and Coma

The term "hepatic coma" has been misused, since it has erroneously included all degrees of cerebral manifestations in patients with hepatic disease. Acute hepatic encephalopathy which may lead to coma is seen at the advanced stage of hepatocellular disease or as part of an episodic encephalopathy to be described later.[4, 6, 10] The usual precipitating factors are protein load in the diet, gastrointestinal hemorrhage, overwhelming infections and diuretics—especially chlorothiazides. In the presence of very severe liver damage such as occurs in fulminating hepatitis, acute liver necrosis or terminal phases of cirrhosis, precipitating factors may not be apparent; the encephalopathy and coma are simply the final outcome of an impaired liver unable to detoxify even small amounts of substances passing through it.

The neurologic picture may develop abruptly, but more commonly there is a stage of gradual and almost imperceptible symptomatology. Early euphoria, depression or slight tremor may suggest the onset of the cerebral complications. This is often followed by an encephalitic picture which is referred to as the stage of impending coma. There is mental confusion, fluctuating changes in the level of consciousness or simply euphoria and lethargy. Tremor or the characteristic "liver flap" may be seen at this time. Flapping tremor is a tremor of action with intention. It is characterized by rapid rhythmic jerks of flexion and extension of the fingers and wrist in bursts of 1 to 2 per second with intervals of 1 to 7 seconds. Flapping tremor is of diagnostic importance but is not pathognomonic of liver disease since it may accompany a variety of metabolic conditions, especially chronic pulmonary insufficiency, cardiovascular decompensation, uremia, etc. As the neurologic involvement progresses, pyramidal tract findings, muscle spasms and seizures may occur. Primitive reflexes such as sucking and grasping make their appearance. Agitation, restlessness or true psychosis may resemble delirium tremens and render the differential diagnosis difficult.[7]

Unless the patient's condition can be reversed, there is a gradual progression to a state of stupor which resembles a deep sleep, from which the patient may be aroused for short periods. Muscle tone and deep tendon reflexes may remain increased while the electroencephalogram shows slowing of the dominant rhythm toward the theta and delta range. The patient may assume bizarre flexor postures, particularly with the legs flexed on the abdomen. Coma follows the stupor and the patient becomes flaccid and completely unresponsive. At this stage, the patient is often deeply jaundiced.

The results of liver function tests in liver coma are generally abnormal but not different from those in cases of severe hepatic disease without coma. Severe electrolyte disturbances, especially hyponatremia, may contribute significantly to the deterioration of the state of consciousness in hepatic failure and should be recognized and treated early. Hypokalemia and hypomagnesemia are equally important complicating factors.[14] Acid base balance was discussed recently by Zieve.[14] Depending upon the severity of respiratory and electrolyte abnormality, one may find respiratory alkalosis, metabolic alkalosis or metabolic acidosis.

The prognosis of acute encephalopathy, especially when deep coma supervenes, is usually poor. This is particularly true in the presence of advanced hepatocellular disease. However, if a definite exogenous precipitating factor is present, vigorous therapy may prove lifesaving.

Episodic Encephalopathy

Bizarre neurologic changes in patients with hepatic disease characterized by shifting episodic disorders of personality, affect and memory, or recurring states of delirium, stupor or coma should suggest a diagnosis of episodic hepatic encephalopathy.[4, 9, 11] Such conditions are encountered more frequently among patients with surgical portal caval shunts or with portal hypertension in whom venous shunts and collateral circulation have developed. These patients may show great intolerance to protein, so that small amounts of protein may induce severe symptoms.

Neurologic signs, including ataxia, tremulousness, flapping tremor, slurred speech, blurred vision, pyramidal tract findings, etc., may sometimes dominate the picture. Repeated episodes of such deficit can occur with complete recovery. However, some patients develop accumulated neurologic residuals.

The prognosis of episodic encephalopathy is good provided that the condition is recognized and treated immediately. At the time of the episode, the patient has increased blood ammonia and responds well to bowel sterilization by nonabsorbable antibiotics and the removal of any other precipitating factors such as severe infection, trauma, gastrointestinal hemorrhage, etc.

Chronic Hepatic Encephalopathy

In this form of the disease severe changes in the state of the sensorium may be absent, although the chronic picture may be interrupted by repeated episodes of stupor or coma. The patient may present a picture of progressive personality change or chronic dementia or may exhibit a mild delirium, restlessness and headache.[4, 11] This chronic syndrome may first be seen as a diagnostic problem in mental hospitals since the mental disorder may dominate the clinical picture. Convulsions, extrapyramidal manifestations and focal neurologic deficit may be present in a small number of cases. Abnormal neurologic signs such as reflex changes and Babinski signs may frequently be seen in the absence of functional impairment. Meningeal signs are extremely rare.

THE ELECTROENCEPHALOGRAM IN HEPATIC ENCEPHALOPATHY. The electroencephalogram in hepatic encephalopathy may show pronounced changes. In impending coma, bilateral slowing of the dominant rhythm is seen from the alpha to the theta rhythms. As the coma progresses, delta waves and later flattening of the record are observed.[1, 3] The triphasic waves that have been considered most typical of hyperammonemia are not always found.

Hepatic Myelopathy and Encephalomyelopathy

Manifestation of spinal cord involvement alone or in combination with cerebral symptoms is relatively uncommon. Pathologic studies have revealed abnormalities in cases in which no clinical correlation could be made,[4] either because the encephalitic symptoms overshadowed the spinal cord findings or because the cord pathology was mild and subclinical. Progressive spastic paraplegia may occur in rare instances.[15]

TREATMENT

Until the cause and pathogenesis of the hepatic encephalopathy are more clearly understood, vigorous attempts should be made to recognize and eliminate factors which cause increase in the production of ammonia in the patient suffering from liver disease. Some of these conditions are gastrointestinal hemorrhages, excessive use of diuretics, intermittent infections, uremia and excessive protein intake in food. Nonabsorbable antibiotics, such as neomycin, are administered up to 4 to 8 grams per day in cases of impending coma. A daily intake of 1500 calories or more provided by administration of 10 to 20 per cent of glucose or partially hydrolized starch is important. In the acute cases, protein intake is completely restricted for two to four days. It is then reinstituted to about 20 to 30 grams daily. As the patient improves, the protein is gradually increased while the antibiotics are continued. If improvement continues, the antibiotics are gradually withdrawn. In general, patients with episodic symptoms tolerate a high protein diet with no symptoms as long as neomycin is continued. Later, moderate or even normal protein intake may be tolerated without neomycin. Repeated enemas are generally administered in acute cases to eliminate the ammonia-producing substances in the gut; or an initial enema may be given, followed by regular bowel movements maintained by magnesium sulfate. Vitamin supplements, especially of the B group, are an important part of the treatment. Arginine glutamate is particularly useful in cases of coma induced by an exogenous agent. It is usually administered with an intravenous infusion of 10 to 15 per cent glucose. Arginine glutamate in the amount of 50 to 100 grams is diluted in 1000 cc. of fluid; this may be repeated two or three times. Particular attention should be given to the state of hydration and to correction of electrolyte deficits. The prognosis in the acute cerebral syndrome is poor if the changes in the state of consciousness persist after one week of therapy.

Prevention of recurrence of episodic stupor involves adjustment of the protein in the diet to the tolerance of the patient. Neomycin may be necessary for an indefinite period of time if satisfactory protein intake is desired. Recently total colectomy with ileorectal anastomosis was suggested since the toxic substances resulting from bacterial degradation of nitrogen residuals are mostly absorbed after they reach the large bowel. This procedure was particularly successful in recurrent hepatic coma following portal caval anastomosis.

SUMMARY

The metabolic defect responsible for the neurologic manifestations in liver disease is poorly understood. Recent work has implicated ammonia as an important etiologic factor, especially in cases of portal caval encephalopathy.

The principal pathologic changes include degenerative neuronal changes mostly in cerebral cortex and basal ganglia and characteristic alterations in protoplasmic astrocytes.

The usual clinical pictures include acute, chronic and recurrent forms of encephalopathies. The acute encephalopathy is characterized by a gradual deterioration of the state of consciousness associated with mild delirium, flapping tremor and other diffuse motor manifestations. Terminally, coma occurs with slowing of the electroencephalogram. In the chronic form, there are progressive personality change and dementia associated with pyramidal and extrapyramidal manifestations. The episodic encephalopathy is characterized by recurrent mental and neurologic deficit and is usually seen with portal caval shunts. Myelopathy as a clinical manifestation is rare.

Therapy is directed toward the elimination of precipitating causes, the use of nonabsorbable antibiotics, the restriction of protein and other supportive measures. Use of arginine glutamate may be tried; it is particularly useful in cases of recurrent encephalopathies associated with portal caval shunts.

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Collagen Diseases and the Nervous System

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THE CONCEPT of the collagen diseases or disorders of diffuse involvement of connective tissue includes the entities of systemic lupus erythematosus, dermatomyositis and polymyositis, periarteritis nodosa, scleroderma, rheumatoid arthritis, Sjogren's syndrome and thrombotic thrombocytopenic purpura.[15, 27, 32] Whether these diseases are intimately related by a single cause or multiple etiologic factors and should be grouped together even though there are morphologic similarities remains a matter of some consideration. In many instances, clinical syndromes are not clearly and definitively delineated, and cases occur which do not fit into any one specific diagnostic category.[15] Many recent studies indicate that the disorders may be due to an abnormal hypersensitivity state or autoimmune process with systemic lupus as the prototype.[32] In these diseases abnormal states of serum proteins develop, especially in the gamma globulin fractions, which are related to antibody activities. The tissue reactions in all involve blood vessels with a vasculitis, and lesions in the general ground substances. Although there are presumably characteristic differences in each condition, the similarities of the lesions may be more significant than more individual patterns.

There has been developing emphasis on transitional or overlap cases,[15] starting as typical dermatomyositis, then developing features of systemic lupus erythematosus and finally terminating with lesions of periarteritis nodosa. A more frequent development is that of systemic lupus erythematosus with signs of dermatomyositis, terminating as scleroderma. The LE factor appears mainly in systemic lupus, but it is absent in 4 to 40 per cent of cases in different series and also may be present in the other diseases. The rheumatoid factor appears in over 30 per cent of the patients with systemic lupus and also in scleroderma, dermatomyositis, periarteritis nodosa and Sjogren's syndrome. Nuclear fluorescence and complement fixation tests demonstrate antinuclear and anti-DNA reacting gamma globulins in all of these diseases. Yet, occasionally an agammaglobulinemia appears in some patients in association with a polyarthritis similar to rheumatoid arthritis, and at times features of scleroderma and dermatomyositis.

Of great interest are studies of the family constellations of various collagen disorders. These are suggestive of a common genetic abnormality.[32] There are reports of different collagen diseases appearing in different members of the same family such as rheumatoid arthritis and systemic lupus as well as agammaglobulinemia. Abnormal gamma globulin factors may appear in the serum of asymptomatic relatives. There is, therefore, the suggestion that there may be an abnormality genetically determined in antibody-synthesizing systems permitting the development of variable inflammatory reactions depending on a particular type of connective tissue antigen involved in the autoimmune response.[32] The type of change, therefore, would depend upon the nature and number of autoantigens (even from normal cell constituents) to which the patient becomes sensitive. The release of antigen in the reaction may be triggered by various factors, in probably predisposed individuals, and these have been considered particularly with regard to systemic lupus and dermatomyositis. Of special importance are the apparent drug-triggering mechanisms in patients treated with hydralazine and the anticonvulsants, trimethadione and diphenylhydantoin.[1] The latter are of importance in consideration of neurologic disorders because of the large population of epileptic patients treated with anticonvulsant drugs. The association of dermatomyositis and polymyositis with malignant tumors[30] and the precipitation of lupus reaction in sunlight[15] are indicative of other triggering factors.

The increasing diagnosis and study of these conditions have led to a greater awareness of the occurrence of significant neurologic manifestations which may assume major importance during the natural history of any of these disorders. The lesions in these diseases are usually secondary to degenerative and proliferative changes in the connective tissue of smaller blood vessels producing mainly occlusion, occasionally rupture, and resultant disseminated ischemic damage and infiltrations in the central nervous system, peripheral nerves and muscles.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic or disseminated lupus erythematosus is usually a prolonged, generalized disease involving collagen tissues throughout the body with acute exacerbations and remissions, occurring mainly in females (85 per cent of cases), most commonly between the ages of 15 and 40.[14, 29] The etiology is unknown; however, a number of cases have been precipitated by exposure to sunlight and general infections as well as by drugs such as trimethadione, diphenylhydantoin and hydralazine.

Pathology

The lesions are primarily vascular (Fig. 1) with fibrinoid degeneration of collagen in small arteries and arterioles, eventually producing conglomerate masses of fibrinoid tissue in the walls, destruction of muscularis and elastic tissue elements and finally occlusion.[8, 18] Endothelial proliferation may contribute toward thrombus formation. Synovial and serous membrane involvement is frequent. The major neurologic lesions are in the brain with disseminated encephalomalacia, especially in the perisulcal regions (Fig. 2).[8] Perivascular hemorrhage is infrequent. The peripheral nerves and spinal cord are involved less commonly by similar lesions.

Clinical Features

The major general symptoms and signs are those of a febrile illness with polyarthritis, characteristic "butterfly" cutaneous lesions of the face, pleural-pulmonary, pericardial-cardiac and renal involvement. Neurologic manifestations[7, 8, 14, 27] include focal and generalized seizures in the absence of azotemia, intellectual deterioration and confusional states, headaches, hemiplegia, aphasia, cranial nerve paralyses and other focal cerebral disorders. A previous history of Sydenham's chorea has been reported.[8] Signs of spinal cord lesions[13] and polyneuritis[24] are

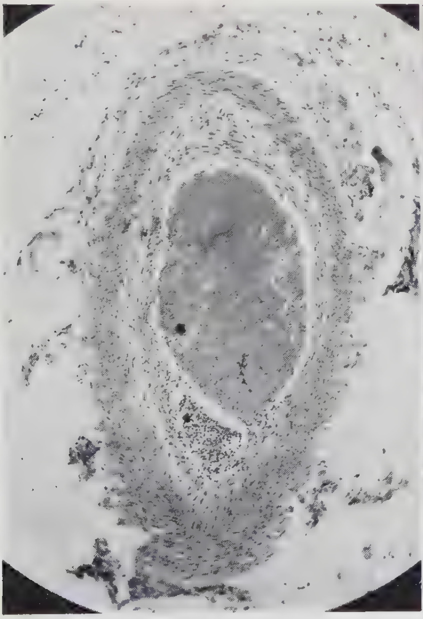

Fig. 1

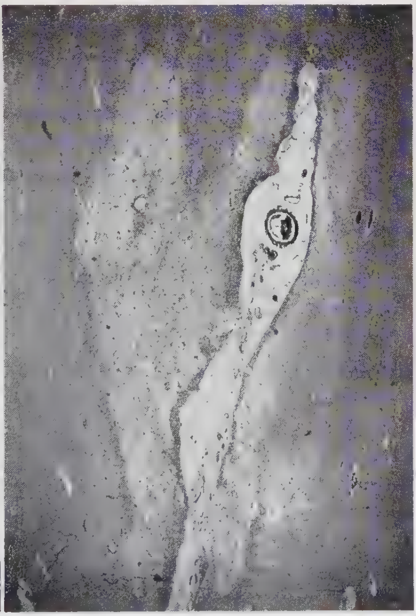

Fig. 2

Fig. 1. Acute systemic lupus erythematosus. Arteriole in meninges with infiltrated wall, fibrinoid degeneration and thrombus. Hematoxylin-eosin stain.

Fig. 2. Acute systemic lupus erythematosus. Perisulcal encephalomalacia in cerebral cortex. Hematoxylin-eosin stain.

unusual. Rarely, an ascending Landry-Guillain-Barré type of polyneuritis may appear. In at least 2 per cent of cases, a convulsive seizure may be the first symptom and during the course of the disease up to 30 per cent of patients may have seizures, 18 per cent may develop other signs of focal nervous system damage and at least 30 per cent may have psychotic reactions secondary to cerebral lesions. Abnormal electroencephalograms with both focal and generalized deviations may appear at least in 50 per cent of cases. Some patients with neurologic symptoms are found not to have structural lesions in the nervous system, and in these cases it is felt that secondary metabolic abnormalities such as azotemia or electrolyte imbalance are affecting neural functioning. By contrast, lesions in the nervous system have been found at autopsy in as many as 50 per cent of the patients in some series without any indications of signs or symptoms involving the nervous system. These lesions usually are small, however.

The neurologic disturbances usually develop in a very active phase of the disease or exacerbation and, once present, are less likely to be involved in a remission. However, nervous system involvement infrequently may precede the more general disease.[27] Acute psychosis with delirium is relatively common, especially terminally, in association with high fever and uremia, and is not necessarily due to specific cerebral lesions. "Papilledema" may be present, with impairment of visual acuity, and is usually secondary to local retinopathy and not increased intracranial pressure.

The cerebrospinal fluid often contains an elevated protein especially in the globulin fractions and occasionally a pleocytosis of up to several hundred lymphocytes. Occasionally an abnormal colloidal gold curve may occur with first zone elevation. Associated hematologic disturbances usually are leukopenia, anemia (normochromic, hypochromic or often hemolytic), and thrombocytopenia with purpura. The erythocyte sedimentation rate usually is elevated. Hyperglobulinemia is common. Anticomplementary or false positive tests for syphilis may be found. The bone marrow and blood usually contain characteristic LE cells.

The course and prognosis of systemic lupus are very variable. At least 20 per cent of patients survive more than five years, 78 per cent surviving at least one year. A spontaneous remission occurs in 40 per cent and may be repeated in 20 per cent. Renal failure and severe intercurrent infection are frequent causes of death.

Treatment

The methods of management or treatment of systemic lupus erythematosus may be regarded as typical of those applied to all the collagen diseases.[11] Specific curative therapy is not available. General supportive measures include bed rest and limitation of activities during exacerbation, local applications to reduce discomfort from cutaneous lesions, control of pain by suitable analgesics, appropriate medical treatment of cardiac and renal failure and antibiotics for complicating infections. Significant suppression of activity of the disease process may be accomplished in many instances by the use of adrenal cortical steroids such as cortisone, prednisone and newer derivatives, as well as corticotropin.[4, 11, 14, 28] High doses should be administered at first and gradually decreased over a period of 10 to 14 days until the maintenance level is reached. In most instances, intermittent or continued maintenance treatment will be required. Typical dosage schedules are: cortisone, initial dosage 200 to 300 mg. a day, with maintenance at 50 to 100 mg. per day; prednisone, initial dosage 40 to 60 mg. per day, with maintenance at 10 to 25 mg. per day; dexamethasone, initial dosage at 6 to 10 mg. per day, with maintenance at 1.5 to 4 mg. per day. It has been stated that 3 per cent of patients need the equivalent of 1000 mg. of cortisone per day (rarely up to 2000 to 4000 mg.) in acute crises of systemic lupus.[4] When high dosages of steroids are used (over a cortisone equivalent of 100 to 200 mg.), adjunctive therapy is necessary such as prophylactic ulcer regimen, diminished dietary sodium to 2 grams or less per day and the administration of potassium salts up to 10 grams per day. The patient should be followed carefully for the development of induced diabetes by determinations of urine and blood sugar and osteoporosis should be watched for by occasional vertebral x-rays. Some workers feel that in about 30 per cent of the cases, steroids are not needed, but these are patients without neurologic abnormalities. In these instances, treatment with rest, salicylates and antimalarial drugs (such as hydroxychloroquine) is warranted.[4] Other medications which have been used less intensively in the treatment of systemic lupus are nitrogen mustard and metabolic analogs such as 6-mercaptopurine, which have no significant effects on neurologic lesions.

Often it is difficult to determine the necessary dosage of steroids. This usually is based upon the intensity of the clinical picture, including the fever and the degree of anemia present, not the positivity of the LE test. Occasionally a problem occurs with reference to cerebral involvement when patients develop psychotic reactions[10] or seizures.[9] It may be difficult to ascertain whether the symptoms are associated with a progression of brain lesions or are merely secondary to the adrenal steroid administration. For example, in one series, 30 per cent of patients had seizures due to cerebral lupus and an additional 5 per cent developed seizures with hormonal therapy; also, at least 30 per cent develop psychotic reactions with cerebral lesions, with potential increase to a 60 per cent incidence during treatment.[28] These reactions are more likely due to active lesions of the collagen disease if the patient has had a recent exacerbation and is febrile; they might be related to hormone administration late in the course of treatment, especially when the "Cushingoid" state is marked.[9, 10] Induced fluid retention, hypertension and potassium deficiency have a relatively poor correlation, however, with these disturbances. In these instances, it is advisable to plan a trial of increased dosage. If the symptoms do not improve after several days of the higher dose level, this should be diminished gradually since rapid withdrawal of steroids may intensify psychotic states. The problem often becomes compounded by the effects upon brain function of secondary metabolic disturbances which often are present such as uremia or electrolyte imbalance, especially hyponatremia.

Because of the essential nature of damage involving the central nervous system, complete reversal of neurologic signs and symptoms usually does not occur even with generally successful effects of treatment elsewhere.

SCLERODERMA

Scleroderma or progressive systemic sclerosis[17] is characterized by focal or generalized thickening and induration of the skin and other tissues, especially certain viscera, particularly the gastrointestinal tract. The disease occurs usually between the ages of 30 and 50 and is more common in females. In many instances there appear to be transitional phases between systemic lupus, dermatomyositis and scleroderma. The etiology is obscure. It has been related to endocrine dysfunction, neurotrophic factors, hypersensitivity and infections, but there have been no definite conclusions.

Pathology

Swelling, proliferation and fusion of collagen fibers as well as fibrinoid degeneration and infiltrations occur in small arteries and arterioles of the skin, skeletal muscles, heart, lungs, gastrointestinal tract and kidneys. Atrophic changes also develop in the skin and mucous membranes. Muscular atrophy and interstitial infiltrations appear as in polymyositis.

Clinical Features

The onset is usually insidious, with fever, focal and diffuse edema in the skin and peripheral vasomotor disturbances, particularly of the Raynaud type associated with sensitivity to cold. Eventually, the characteristic skin changes occur, especially in the face, neck and upper extremities, with a taut thickening and a shiny, waxy appearance associated frequently with pigmentary variations, erythema and loss of hair. Limitation of motion and contractures are frequent; facial mobility is lost. Trophic ulcerations are common, especially in the fingers and toes. The involved muscles are tender, indurated and atrophic. Hoarseness and dysphagia may develop. A mild peripheral neuropathy results in paresthesias and sensory deficits. Central nervous system lesions are rare and when they occur probably are vascular in origin as in other collagen disorders; in these instances, the patient may be in a transitional phase with systemic lupus.

Diffusely abnormal electroencephalograms have been found in a number of patients with scleroderma but are without other clear clinical correlations. The cerebrospinal fluid is usually normal. Other systemic symptoms more commonly relate to joint, gastrointestinal tract and cardiopulmonary involvement. The prognosis generally is poor, at least 50 per cent of the patients dying within five years and the surviving 50 per cent having a prolonged course with debilitation and recurrent infections.

Treatment

No specific treatment is available. In addition to general supportive measures, physical therapy may be necessary to help prevent and overcome deforming contractions. Corticotropin and adrenal steroids may be used as in the treatment of systemic lupus, but the results are much more inconstant and often transitory. Potassium para-aminobenzoate has been found effective in some series, but without permanent results. Cervical dorsal sympathectomy may give temporary benefit in cases with severe vasomotor disturbances in the extremities but does not produce regression of lesions.

POLYMYOSITIS AND DERMATOMYOSITIS

This disorder basically, as polymyositis, is an acute and chronic disease of skeletal muscle characterized by degenerative and inflammatory reactions, both in the muscle fiber and its supporting collagen-connective tissue. The condition may exist alone, involving just muscle without any major systemic involvement and as such may be within the group of primary myopathies.[5, 21, 30] However, many instances of polymyositis are associated with more generalized collagen disease. These include not only myositis with cutaneous lesions as dermatomyositis, but also with clinical features, particularly visceral and articular, of other collagen diseases such as acute systemic lupus, scleroderma, rheumatoid arthritis, periarteritis and Sjogren's syndrome.[26] In addition, a significant number of cases (up to at least 25 per cent in various series) have been associated with malignant disease elsewhere, as "carcinomatous myopathy."[30]

Etiology

Polymyositis existing alone may represent a localized disorder of collagen tissue within the muscle. As such, the condition is regarded to be of unknown etiology, but it may be related to a hypersensitivity mechanism, as is being considered in many of the collagen disorders. There is little indication yet of a definite familiar or hereditary basis.

The instances appearing in association with malignant disease may be related to a peculiar immunologic reaction or metabolic competition; however, no definite etiologic factors have been brought to light. Some cases are known to follow infections and these are to be differentiated from polymyositis due directly to known infection in the muscles such as trichinosis, toxoplasmosis, bacterial and certain virus (such as Coxsackie) diseases.

Pathology

The histopathologic lesions in polymyositis are of significance since both diagnostic and prognostic determinations may be obtained from muscle and skin biopsy.[26,30] The arterioles in the skin, subcutaneous tissues and muscles show thickened walls and infiltrations. In some cases, however, vascular lesions are minimal. Cutaneous edema, atrophy and infiltrations also develop. The skeletal muscles (Fig. 3) contain both degenerative and regenerative changes in random fibers with necrosis, segmental fragmentation and atrophy of fibers, vacuolization, great variation in fiber size, phagocytosis, proliferation of sarcolemmal nuclei, and eventual fibrosis with increase in endomysial collagen. Intense basophilia may indicate regeneration. Interstitial infiltrations are usually considerable and consist of lymphocytes, monocytes, plasma cells, eosinophils and rarely leukocytes, usually, but not always, in a perivascular distribution, and occasionally nodular. The intensity of the degenerative and infiltrative lesions varies according to the acuteness of the disorder.

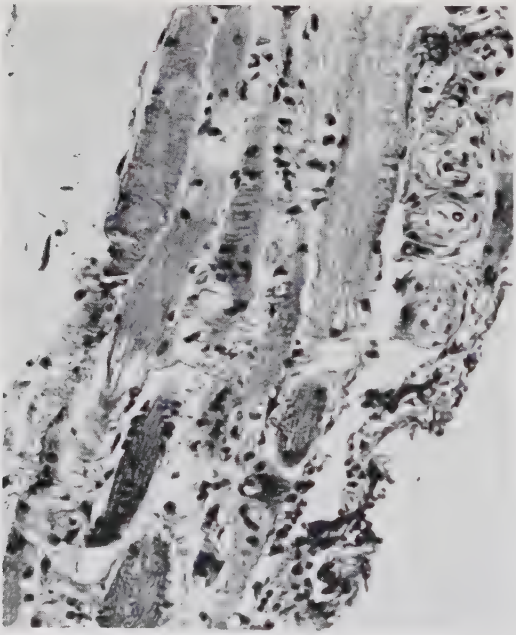

Fig. 3. Dermatomyositis. Necrosis of skeletal muscle fibers, some basophilic; proliferation of sarcolemmal nuclei; infiltrations. Hematoxylin-eosin stain.

The terminal nerve fibers may develop complex arborizations, and dysplastic and degenerative changes may be found involving the motor end plates.

Muscle biopsy is useful in establishing categorical diagnosis, but patchy muscular involvement may be misleading, and the findings in certain stages are nonspecific. In the more chronic instances, there may be great difficulty in distinguishing this disorder from a chronic muscular dystrophy, especially when the fibrosis is extensive. Lesions of polymyositis, however, differ from the specific patchy necrotic infarctions of the muscles in periarteritis nodosa or the characteristic nodules of sarcoid myopathy. Rarely, vascular lesions are present in the brain, and when these are found, the case may represent a transition between dermatomyositis and acute systemic lupus.

Clinical Features

Polymyositis has a widespread incidence from infancy to old age, but appears mainly between the ages of 10 and 50 and is twice as common in females. The actual prevalence of this disorder is not known since many cases appear as variants within the larger group of the collagen disorders.

Acute polymyositis and dermatomyositis are frequently seen in children but also occur in adults. The onset is usually insidious, with fever, patchy cutaneous erythema and edema, myalgia, weakness, arthralgia and vasomotor disturbances. The skin manifestations, when present, are diverse and characteristically appear first in the face, especially about the nose and cheeks, often with a light purple or "heliotrope" hue. The upper extremities then may become involved, especially the extensor surfaces of the hand and the nail beds. Raynaud's phenomena are frequent and ulcerations of the fingers often occur. Skeletal muscle disorder may precede, follow or exist without the presence of skin lesions. Any striated muscle may become involved; typically, proximal symmetric weakness appears involving the shoulder and pelvic girdles with or without muscle tenderness, but usually the muscles become tender, somewhat swollen and indurated. In some instances, the skin lesions may be inconspicuous and exist only as telangiectases or patches of scleroderma-like lesions on the extensor aspects of the forearms, hands and face. At times, one sees only hyperemia of the fingertips and periungual regions. Eventually, facial, jaw, pharyngeal and distal skeletal muscles become involved.

Dysphagia appears in over one half of the cases, but ophthalmoplegia is rare. In severe instances, respiratory paralysis ensues. Atrophy is variable and visible fasciculations are extremely unusual. Myasthenic and myotonic phenomena may be found, but response to neostigmine is minimal. The deep reflexes, normal at first, eventually become inactive. Contractures often develop in chronic instances. Distal sensory deficits have been reported as rare occurrences, probably related to neuropathy secondary to an associated collagen disorder such as lupus or periarteritis.

In polymyositis and dermatomyositis, general systemic involvement is somewhat unusual, but it may occur with hepatosplenomegaly, lymphadenopathy and evidence of cardiac disorder or pericarditis. Electrocardiographic abnormalities, however, are relatively frequent. Renal involvement is unusual, but may be associated with albuminuria and rarely, uremia. In up to 50 per cent of cases, however, mild to moderately severe joint involvement may occur with indications of arthralgia and arthritis along with effusions, particularly at the fingers and wrists.[21] Recurrent bursitis of the shoulders and hips has been found. Retinal edema and hemorrhages rarely occur.

The intensity of the symptoms often fluctuates a great deal. In some instances, a relatively benign course over many weeks leads into slow, perhaps fairly complete recovery. Severe involvement in the early stages may produce later deforming muscle contractures. Less frequently, the course is fulminating with severe dysphagia and respiratory difficulties. In more chronic states of polymyositis and dermatomyositis, there is a slowly progressive weakness and wasting of proximal muscles of the upper and lower limbs; it gradually becomes more severe with the slow development of distal weakness as a "late onset myopathy."[26] A waddling gait often ensues and steps are negotiated with increasing difficulty. Muscle tenderness and pain are frequently absent; in these instances, differentiation from progressive muscular dystrophy is difficult.

The electromyogram often shows significant muscular irritability, with increased numbers of low-amplitude polyphasic discharges on voluntary contraction and occasional myotonic-like, repetitive discharges. Fasciculation and fibrillation potentials are rare. These findings are not specifically diagnostic of polymyositis, but their presence is highly suggestive. Electromyographic abnormalities have appeared in 25 to 65 per cent of the cases in various series.

There are a number of important chemical and hematologic abnormalities.[21, 30] In some instances, the muscular degeneration produces myoglobinuria and, more frequently, a nonspecific creatinuria. The pathologic process involving the muscle fibers causes a release of various enzymes which then may be present in elevated quantities in the blood serum. Levels of these enzymes may indicate the degree of activity of the myositic process and may be valuable as guides in diagnosis, prognosis and therapy. They are highest in acute or subacute myositis and often are low or normal in chronic myositis. Remarkably high levels of serum transaminase (over 400 units) may be present. Elevations of aldolase, dehydrogenases and creatine kinase also may be found. Increased levels may be found also in some cases of active muscular dystrophy, but usually not to the heights present in myositis. Hematologic changes include either leukocytosis or leukopenia, anemia, eosinophilia rarely, elevation in erythrocyte sedimentation rate and hyperglobulinemia, the latter changing the electrophoretic pattern of proteins in the serum in up to 70 per cent of the cases. A latex fixation test usually is positive when there are signs of arthritis, and a rheumatoid factor test has been positive in up to 50 per cent of cases.[21] Renal involvement may be present with albuminuria, but severe states of renal decompensation are unusual in this disease. Although an elevated basal metabolism rate occurs relatively frequently, there is no clear-cut evidence of thyroid dysfunction. The reason for this elevation is not clear.

Generalized osteoporosis, subcutaneous calcinosis and skeletal deformities appear in advanced cases. Calcium deposits may appear three to five years after the onset of the disease in subcutaneous tissue, in tendons and in muscle itself.[19] These may be particularly extensive in children. This type of calcification, as a complication or sequel of polymyositis, should be differentiated from progressive myositis ossificans. The disorder in polymyositis is a precipitation of calcium deposits in relation to the inflammatory and degenerative disorder in the muscle and connective tissue. Myositis ossificans is a different process with eventual formation of true bone tissue in the fascial planes of connective tissue within the muscles. Lesions similar to those of polymyositis are not found.

The course in polymyositis and dermatomyositis is extremely variable, with remissions and exacerbations. Peak developments usually occur within the first year, but 50 to 60 per cent of patients usually die within two years and the remainder experience spontaneous complete remissions or residuals with permanent atrophy, weakness and contractures. The prognosis is more grave in the older age groups.

Treatment

Specific curative therapy is not available since a definite cause usually is not known. General supportive measures include bed rest, limitation of activity and the use of analgesics for muscle pain, especially salicylates. Significant suppression of activity of the collagen disease process may be accomplished by the administration of adrenal cortical steroids and corticotropin. As in treatment of acute systemic lupus, dosages of hormone, necessarily high at first, should be decreased gradually. In most instances, continuous or intermittent maintenance treatment is required, and it often is possible to maintain the patient in a fair state of remission successfully on low dosages of hormone for long periods of time. Probably every patient with active polymyositis or dermatomyositis should receive several weeks or even months of such therapy before cortical steroids are dismissed as of no value. Close supervision is necessary to minimize the secondary effects of hypercortisonism. The fluorinated corticosteroids such as triamcinolone should be avoided in the treatment of polymyositis since these have been found to induce severe weakness and an atrophic degenerative myopathy, so-called steroid myopathy.[31] This occurs less frequently with prolonged hydroxycorticosteroid administration. In general, the clinical response to hormone therapy is quite variable; some cases, particularly the more acute, may be relieved remarkably, but others relatively poorly. A limiting factor is muscle fibrosis, which is more prevalent in chronic cases.

POLYMYALGIA RHEUMATICA

An illness with disseminated muscular pain and generalized symptoms is now frequently recognized as afflicting middle-aged and elderly persons.[12] The cause is obscure but the condition has been regarded as a "rheumatoid variant" and also is called "anarthritic" rheumatoid disease. It is over three times more common in women and appears between the fifth and eighth decades. No specific lesions have been found in the muscles or other tissues; however, occasionally perivascular infiltrations with chronic inflammatory cells have been found in muscle. A relationship to "giant cell arteritis of the aged" has been suggested.

The onset most often is sudden, pain and stiffness appearing in the neck and shoulder girdle muscles and spreading to the lumbar, gluteal and thigh groups. Distal portions of the extremities usually are spared. Tenderness is minimal and muscle weakness does not appear, disability being related to stiffness and pain. The periarticular tissues may become involved but actual joint swelling is rare. Along with these symptoms the patients usually experience headache, slight fever, sweating, anorexia, weight loss, malaise and depression. The erythrocyte sedimentation rate characteristically is elevated to over 100 mm. along with a normochromic anemia and increases in serum albumin, globulins and fibrinogen. The leukocyte count is usually normal or only slightly elevated. Infrequently, serum abnormalities may be present without the muscle pains. The course is fluctuating, with remissions and exacerbations. Most often the disorder is self-limited and there is gradual relief, but only after a few months or years of symptoms. This condition is to be differentiated from polymyositis (mainly by the absence of weakness and histologic lesions), dermatomyositis, rheumatoid arthritis, systemic lupus, carcinomatous myopathy, cervical and lumbar disc syndromes and various other arthritic disorders. Although the illness is relatively benign and self-limited, the disability may be severe and active therapy is warranted. Bed rest and salicylates are helpful in relieving the pain. Rapid, striking improvement may be achieved by the administration of adrenal cortical steroids in moderately high dosage in short courses, repeated if necessary.

PERIARTERITIS NODOSA

Periarteritis nodosa is a subacute or chronic systemic disease due to a necrotizing arteritis within joints, muscles, viscera and the nervous system. It is at least four times more common in males and occurs from infancy to late adult life, but especially between the ages of 20 and 40. The cause is unknown; however, a hypersensitization reaction may be involved, since in some patients, the disease apparently has been produced by sensitization to heterologous serum or to drugs such as sulfonamides, penicillin and diphenylhydantoin. In most clinical instances evidence of sensitization is not present.

Pathology

The basic lesion is an inflammatory reaction in the walls of small arteries and arterioles with infiltration by polymorphonuclear leukocytes, lymphocytes and eosinophils, a true panarteritis (Fig. 4). Necrosis of muscle and elastic fibers in the vessel walls causes formation of multiple small swellings with rupture or fibrosis, and proliferation of intima often leads to thrombosis. The fibrotic process produces nodules along the arterial wall. There may be slight involvement of veins as well. In contrast to systemic lupus, the vascular lesions of periarteritis commonly involve the vasa nervorum of peripheral nerves causing a polyneuropathy. Focal lesions in cerebral parenchyma also occur, but spinal lesions

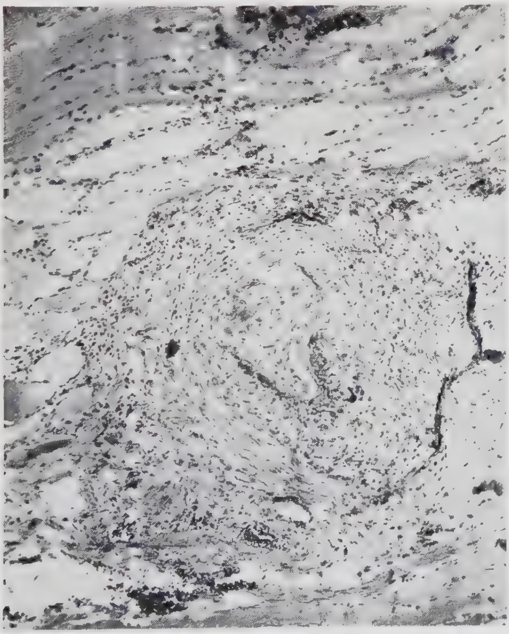

Fig. 4. Periarteritis nodosa. Myositis with involved arteriole showing heavily proliferated, infiltrated wall. Hematoxylin-eosin stain.

are uncommon. Rarely, the large vessels may be involved, in contrast to other collagen diseases, and rupture of a basilar artery, subarachnoid hemorrhage and thrombosis of an internal carotid artery have been attributed to periarteritis nodosa. In general, the infarctive and necrotic lesions in this disorder tend to be larger and more circumscribed than in the other collagen diseases.

Clinical Features

This disorder has an extremely varied symptomatology.[23] The onset may be abrupt or insidious, and early general manifestations are fever, weight loss, dyspnea, cough, malaise, headache, tachycardia, generalized weakness and pains in joints, muscles and abdomen. Further progression may involve any region of the body such as the skin with purpura, nodular and erythematous lesions; the kidneys with hematuria and uremia; the cardiovascular system, with hypertension and pericarditis; the pulmonary system, with asthma, hemoptysis and pleuritis; and the gastrointestinal system, with nausea, vomiting and diarrhea. Anemia, leukocytosis or leukopenia, eosinophilia and hyperglobulinemia occur. Focal and disseminated central and peripheral nervous symptoms[22] appear at onset and often during the course of the disease, with headache, aphasia, hemiplegia, visual deficits, cerebellar signs, seizures, cranial nerve paralyses and personality changes. The peripheral nerves often are involved, in about 50 per cent of cases, with either a generalized polyneuritis or a mononeuritis multiplex; occasionally, an ascending Landry-Guillain-Barré type of paralysis occurs. The cerebrospinal fluid is usually normal, although elevated protein may be present reflecting a polyneuritis; unusually there may be evidence of meningeal hemorrhage.

At least 50 per cent of patients with periarteritis nodosa have a remission of up to several years' duration, appearing usually in the first two years. A duration of two years or more indicates a better prognosis. The prognosis is more grave when renal and central nervous system lesions exist.

There are two special forms of periarteritis with neurologic complications. In one, temporal arteritis, the disorder may be limited to one or both temporal arteries or it may be a predominant involvement in a more generalized periarteritis.[2, 16] However, the late onset of the local lesion, occurring usually between the ages of 60 and 80, and the presence of giant cells in the nodules around the blood vessels make it a more unique syndrome. Symptoms are localized headache, fever, anorexia, tenderness and nodularity of the temporal artery, blindness (in up to 50 per cent of cases) and rarely, diplopia. The course is variable and often is self-limited, resolution occurring in 6 to 12 months. However, the danger of loss of vision is critical and is an urgent therapeutic indication.[2]

The other unusual neurologic syndrome in periarteritis nodosa is characterized by the association of interstitial keratitis, bilateral vestibular symptoms and deafness in young adults with no evidence of syphilis.[3]

Treatment

There is no specific therapy. The principles of supportive management and suppressive therapy with corticotropin and adrenal cortical steroids, as described for systemic lupus, also apply to periarteritis nodosa. However, in periarteritis, healing of vascular lesions may occur with a great deal of intimal proliferation, resulting in further obliteration of the small blood vessels and progressive ischemia and infarction of tissues, despite satisfactory general responses. The changes may occasionally aggravate already existing central nervous system and renal symptoms.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis has been included in the group of collagen diseases. It may exist as a separate entity or in close association as a syndrome with other collagen diseases, particularly systemic lupus erythematosus. In rheumatoid arthritis, a systemic disorder develops, of unknown cause, in which symptoms of inflammatory origin appear in the joints and related structures. The course is extremely variable and chronic, with remissions and exacerbations. It occurs more commonly in women and may appear in infancy and later life, but particularly between the ages of 30 and 40. The inflammatory changes occur especially in joints, with edema, proliferation of capillaries and infiltration producing granulation tissue and fibrosis. Subcutaneous nodules occur consisting of granulation tissue and inflammatory cells as well as necrotic fibrinoid material. Atrophy and degeneration of muscle fibers are prominent, especially around involved joints, with focal nodular infiltrates (Fig. 5) of lymphocytes in the endomysial and perimysial connective tissues. Characteristic muscular symptoms and signs of polymyositis may develop in these patients. It is difficult at times to determine whether the muscular wasting, especially around involved joints, is due to actual polymyositic lesions or the perhaps more common disuse atrophy. Often, histologic lesions of interstitial myositis in this disorder may produce no symptoms or signs referable to muscles apparently so involved. Certainly, symptoms of aching, tenderness and stiffness in muscles appear early in rheumatoid arthritis and remain prominent throughout the course of the disease. In addition, it is recognized that many patients with rheumatoid arthritis have intermittent paresthesias in the extremities, but objective neurologic deficits rarely have been found. In some patients with rheumatoid arthritis, mechanical compression has been thought to be causative of these symptoms, such as tenosynovitis or thickening at the carpal tunnel producing compression

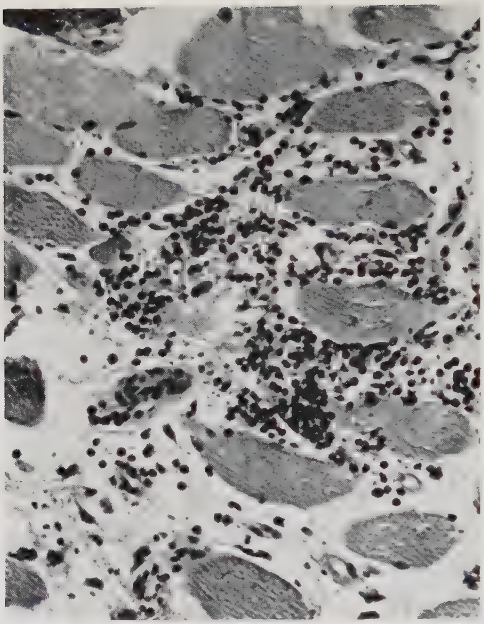

Fig. 5. Rheumatoid arthritis. Nodular interstitial myositis with lymphocytic infiltrations. Muscle fiber atrophy. Hematoxylin-eosin stain.

of the median nerve, or other pressure syndromes on the vulnerable ulnar or peroneal nerves.

It has been recognized for some time that certain patients with apparently classical rheumatoid arthritis develop features of a more generalized disease, often with signs of severe peripheral neuropathy.[2, 25] In these patients a special relationship with a generalized arteritis has been emphasized recently, as well as an association of the syndrome with hypercortisonism. In these instances, one can exclude nerve compression syndromes and other more clear causes of peripheral nerve involvement such as diabetes. The type of peripheral neuropathy present has been divided clinically[6] into two varieties: (1) a symmetric, distal, fluctuating, generalized neuropathy, either sensory alone or mixed motor and sensory and (2) persistent mononeuritis affecting one or several peripheral nerves in two or more extremities, the so-called mononeuritis multiplex. In a number of instances, the two types of involvement may coexist. These two patterns of peripheral neuropathy also are described in patients with diabetic neuropathy, as well as the neuropathy of vascular origin in periarteritis nodosa. The prognosis appears to be more severe in patients with extensive mononeuritis multiplex rather than the more symmetric types of involvement.

The lesions involving the peripheral nerves are usually those of a severe necrotizing arteritis of the nutrient vessels. This may appear de novo or as rapidly developing necrosis in a previously existing, but nondestructive, form of arteritis. Along with this reaction the patients may experience low-grade fever, severe anemia and leukocytosis. Ordinarily, there is no exacerbation of joint symptoms and it would seem that the reactions are limited to the inflammatory involvement of tissues relating to peripheral nerves. The severity of the neuritis often develops in one day, and the course then becomes gradual during the ensuing year, after which recovery is possible. In one series, the continued administration of corticosteroids produced no apparent inhibition of the recovery process. More severe fatal reactions have been described in patients with signs and symptoms of a more generalized arteritis. High values of serum rheumatoid factor were present in these patients as well as positive LE cell tests.

The incidence of this disorder is not high. For example, 64 cases were found within a total population of patients with rheumatoid arthritis at the Mayo Clinic between 1949 and 1959 of over 18,000.[6] In another series, 16 patients were described, as well as 39 from the literature, but incidence or prevalence figures were not given.[25]

The duration of the rheumatoid arthritis before the onset of polyneuritis has varied from one to more than 25 years. Most of the patients have had rheumatoid arthritis for more than five years. In many, steroid therapy had been administered and was regarded as being contributory in the causation of the necrotizing arteritis and the subsequent polyneuritis. This has been emphasized particularly by one group.[6] However, others have felt that the relationship between the steroids and the precipitation of arteritis and neuritis is not convincing. There is suggestive evidence that administration of steroids may promote transformation of a non-necrotizing to a necrotizing arteritis. However, at least one third of the patients developing peripheral neuritis in this syndrome did so prior to the administration of steroids and the development of hypercortisonism.[25] Because of the possible relationship, however, the question of continued administration of steroid in the involved patient is a difficult one to decide. It has been considered worth while to increase the dose temporarily in order to determine whether the vascular lesions may be suppressed thereby, but in general, it is regarded that these patients with arteritis and rheumatoid arthritis are extremely sensitive to manipulation of dosages of steroids. In a number of instances, increase of symptoms developed with reduction of steroids even though hypercortisonism was regarded as contributory. Steroid dosage, then, could not be decreased even though a critical state existed. The mortality rate in these series has varied from 10 to 15 per cent.

SJOGREN'S SYNDROME

The syndrome described by Sjogren in 1933 is now included within the group of collagen disorders. It is characterized by a dry, keratoconjunctivitis with hypofunction of the lachrymal glands, decreased salivary gland secretion and an arthritis similar to rheumatoid arthritis.

These clinical features have been found in association also with lupus erythematosus, scleroderma and periarteritis nodosa. A number of patients have increased gamma globulin in the serum, positive rheumatoid factors, as well as other laboratory test indications considered to be within the collagen disorder group. Recently, a number of patients have been found with Sjogren's syndrome and a generalized myopathy occurring in later life[26] between the ages of 35 and 65. Characteristic features were proximal weakness and wasting of muscle as well as histologic evidence of polymyositis and electromyographic indications of a primary inflammatory myopathic process. There were no indications of central nervous system involvement. Therapeutic results with adrenal steroids in this syndrome are not remarkable.

THROMBOTIC THROMBOCYTOPENIC PURPURA

This is an unusual disease, having an association of thrombocytopenic purpura, hemolytic and frequently neurologic symptoms and signs.[20] The disorder is usually acute, but may be relapsing in rare chronic instances. It may be within the group of collagen diseases, and transitional cases to acute lupus have been found sporadically and in certain families.

Pathology

The lesions in the nervous system consist of hyperplasia of the small arteries, arterioles and capillaries with fibrinoid depositions in the walls and thromboses producing foci of neuronal damage, mainly within the cerebral cortex, basal ganglia and brain stem. Occasional lesions occur in the white matter. Petechial hemorrhages also may be found. Vascular lesions similar to those of systemic lupus have occurred in the kidneys of these patients.

Clinical Features

The general symptoms are those of acute hemorrhage into a region of the body and those of hemolytic anemia, with fever, abdominal pain, nausea, vomiting or arthralgia, malaise, headaches and jaundice. The neurologic disturbances consist of alterations in the states of consciousness with restlessness, confusion, delirium, stupor and coma, focal signs such as hemiplegia, aphasia, apraxia, cranial nerve palsies, focal and generalized seizures and papilledema. These signs and symptoms are due to both the thrombotic and hemorrhagic lesions occurring within the involved areas of the brain.

Treatment

No satisfactory treatment is available. Splenectomy, multiple transfusions and the use of corticotropin and adrenal cortical steroids have been of unpredictable value and usually have not stopped the inevitable progression of the disease.

SUMMARY

There has been increasing awareness of the involvement of the central nervous system, peripheral nerves and muscles in the group of disorders categorized as collagen diseases. These include acute systemic lupus erythematosus, dermatomyositis-polymyositis, scleroderma, periarteritis nodosa, Sjogren's syndrome, rheumatoid arthritis and possibly thrombotic thrombocytopenic purpura. Each of these conditions has its own special clinical and pathologic characteristics; however, there is an underlying constancy of certain lesions such as arteritis and involvement of connective tissues. These and various alterations in reactive proteins, such as the gamma globulins, have led to the consideration that the basic etiology is one of hypersensitivity and an autoimmune process. Overlapping syndromes exist in many patients and certain family constellations contain different collagen disorders rather than a single one in various members. The neurologic and neuromuscular lesions in these disorders are usually secondary to degenerative and proliferative changes in connective tissues and smaller blood vessels producing occlusion or rupture and result in disseminated ischemic damage and infiltrations. There is an unexplained differential involvement of neural structures in the different disorders. In systemic lupus, there are primarily disseminated focal lesions in the brain, with little involvement of spinal cord, peripheral nerves and muscles. In periarteritis nodosa, there is a more diffuse involvement in the nervous system, including the spinal cord, and high incidence of peripheral neuropathy and muscular lesions. The lesions of dermatomyositis and polymyositis primarily are muscular with only a minimal incidence of central or peripheral nervous system involvement. In scleroderma, peripheral vascular disorder may be prominent with a sympathetic nervous component and the occurrence of Raynaud's phenomena, but only infrequently an involvement of central nervous system and muscles. Actually, in scleroderma and dermatomyositis, when central nervous system involvement is present, the possibility of a transitional systemic lupus is considered likely. An unusual and severe polyneuritis may develop in rheumatoid arthritis with arteritis.

Therapeutic considerations have emphasized the effect of hypercortisonism induced by the use of adrenocortical steroids and corticotropin. These treatments are only suppressive and not biologically curative. They are difficult to evaluate because of the variations in the natural history of collagen disorders and spontaneous exacerbations and remissions. However, it is felt that their administration is useful particularly in controlling the spread and the intensity of the disease process. Certain neurologic complications of hypercortisonism such as occurrence of organic psychotic reactions, convulsive seizures and muscular weakness are emphasized particularly in the light of their similarity to effects of collagen disorders upon the nervous system, and they present problems in therapeutic management.

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Diagnosis and Management of Extracranial and Intracranial Vascular Disease

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IN AN ARTICLE published in this journal in 1953, I reviewed the diagnosis and treatment of acute intracranial vascular lesions.[1] It is interesting to reflect on the happenings of the past decade and to try to determine what progress, if any, has been made during that time.

Intracranial lesions of vascular origin still constitute the third most frequent cause of death in the United States.[2] There is no particular solace in the knowledge that diseases of the heart continue to occupy first place and malignant neoplasms second. So far as the major diseases of the heart and blood vessels of the brain are concerned, atherosclerosis continues to be the most important etiologic factor. It is evident that if and when some precise method for the control of atherosclerosis is found, the incidence of these serious disorders will be materially reduced. Until that time we will approach the problem indirectly.

The events of the past ten years have not been entirely discouraging. There has been a revival of interest on the part of the neurologists, neurosurgeons, pathologists and internists. Support for cooperative projects has been generous; four large cooperative studies have been supported. A number of conferences have been carried out at a national level.

Specifically, there is now a better understanding of the role of extracerebral factors in the production of cerebrovascular complications, particularly in the disorders of the large vessels of the neck. Intermittent insufficiency syndromes have been delineated. Careful studies have been carried out in the realm of anticoagulant therapy, and the role of anticoagulants has been scrutinized in the management of ischemic disorders of the brain. Angiography of the aortic arch, the neck vessels and the intracranial vessels has contributed tremendously to our understanding of occlusive disease of the large vessels supplying the brain and to our understanding of the several important causes of subarachnoid hemorrhage. Many articles have appeared in the literature in the past ten years. Yet, vascular diseases of the brain remain the third most common cause of death in the United States!

There is considerable merit to the broad differentiation of cerebral vascular disease into occlusive and hemorrhagic varieties. The first type, in turn, can be subdivided into thrombotic and embolic groups. The second, or hemorrhagic variety, comprises two main groups, hypertensive cerebral hemorrhage and subarachnoid hemorrhage. This is a useful classification for approaching the patient clinically and encompasses the majority of "strokes." Further diagnostic tests and therapy are dependent to a considerable degree upon the specific pattern into which the case falls.

Understanding of the anatomy and physiology of the heart, the aortic arch and the great vessels of the neck is necessary for the appreciation of many of the factors which are involved in the problem of occlusive cerebrovascular disease. Collateral circulation may be effected through the neck vessels, the circle of Willis and the anastomotic system represented by the pial vessels. Although much is known about the vascular supply to the brain, particularly with the increased utilization of angiography, a great deal more information must be acquired before we can appreciate the specific factor which is responsible for the vascular episode in question.

There is a surprising adaptability of the cerebral circulation through the circle of Willis. Anatomic variations in the circle appear to be very important in those situations in which collateral circulation is inadequate.[3] The normal rate of cerebral blood supply considerably exceeds the usual cerebral metabolic requirements.[4] Thus, there is an unusual tolerance of ischemic effects produced by narrowing of vessels until cumulative obstructions reduce the effective flow of blood below tissue demands in some areas and only marginally in others.

The clinical features of cerebrovascular disease are infinitely variable and complex. These are reviewed by Fazekas et al.[4] and include the following: (1) cerebral oxygen delivery, (2) functional completeness of the circle of Willis, (3) collateral blood sources (extra- and intracranial), (4) intracerebral vasodilatation, (5) single or multiple aorto-cranial lesions, (6) speed of development of lesion(s), (7) systemic circulatory dynamics, (8) size of lesion.

Many extracranial disorders are implicated in the production of ischemic cerebrovascular episodes which are manifested as intermittent insufficiency syndromes[5] or as cerebral thrombosis and cerebral embolism. These are listed in outline form:

- I. General and systemic factors
  - A. Systemic hypotension

    Systemic hypotension of sudden onset may occur in the course of many disorders. Usually, localized vascular narrowing must be present additionally to produce focal cerebral phenomena. Causes are:

    1. Hemorrhagic shock
    2. Antihypertensive drugs
    3. Postural hypotension
    4. Postsympathectomy hypotension
    5. Surgical procedures and anesthesia
    6. Gravitational states (aviation)
  - B. Hypertensive vascular disease
    1. Accelerated development of atherosclerosis
  - C. Other disorders
    1. Diabetes mellitus
    2. Hypothyroidism
    3. Hypercholesteremia
    4. Polycythemia vera
    5. Anemia
- II. Cardiac disorders
  - A. Coronary occlusion and myocardial infarction
  - B. Congestive heart failure
  - C. Cardiac arrhythmias
    1. Abnormalities of cardiac impulse formation
    2. Disturbances of cardiac impulse conduction
  - D. Carotid sinus compression
    1. Occlusive effects
    2. Cardiac effects
  - E. Operations on the heart
- III. Diseases of the aorta
  - A. Dissecting aneurysm
  - B. Aortic arch syndromes
    1. Granulomatous arteritis (Takayasu's disease)
    2. Atherosclerosis
- IV. Disorders of the subclavian, carotid and vertebral arteries
  - A. Atherosclerosis
  - B. Complications of angiography
  - C. Giant cell arteritis
  - D. Cervical spondylosis
  - E. Aneurysms
  - F. Head and neck manipulations; other trauma
  - G. Cervical rib

The clinical manifestations are often found in the brain regardless of whether the source is extra- or intracerebral. Often a number of factors are operative.

OCCLUSIVE CEREBROVASCULAR DISEASE

Cerebral Thrombosis

The third Princeton Conference on Cerebral Vascular Diseases[6] was devoted primarily to a discussion of the three varieties of ischemic strokes, namely, the incipient or impending stroke, progressing and completed stroke.

Focal intermittent insufficiency or ischemic attacks are better understood through the clinical description of Millikan and colleagues.[7] These are transient episodes of focal neurological dysfunction. Clinically they can usually be attributed to diminution of the blood supply through the carotid or the vertebral-basilar systems. The cause is not well understood. Fibrin clots may form and a portion of the clot may break off and enter the arterial circulation as an embolus; or an atherosclerotic plaque may so reduce arterial flow through the vessel that any circumstance that reduces cardiac output or arterial pressure may suddenly result in further diminution of circulation in the area supplied by the diseased vessel. The concept of "vascular spasm" to explain these episodes has not gained acceptance.

The term "progressing ischemic stroke" is self-explanatory. Very often the patient will have experienced warning episodes in the form of intermittent insufficiency episodes. The point has now been reached where the situation is no longer reversible. Thrombosis usually requires a number of hours or several days to develop.

The completed thrombotic stroke is one in which the ischemic events have occurred and the neurological deficit is present; if the patient survives, there is a tendency for improvement of the condition. Thus, variable degrees of disability may remain. Occasionally the situation reverses satisfactorily.

Cerebral Embolism

Cerebral embolism is distinguished by an abrupt onset, by dramatic alterations in the state of responsiveness, and by severe impairment of motor and sensory functions. The incidence of cerebral embolism varies appreciably in the reports of various authors. For example, Aring and Merritt[8] reported an incidence of approximately 11 per cent of their cases. Groch et al.[9] reported an incidence of 36 of 688 cases, a surprisingly low figure of 5 per cent. The cooperative clinical study of Baker et al.[10] listed approximately 7 per cent of their cases as embolic and an additional 25 per cent as "thorem," a contraction of "thrombosis-or-embolism."

The source of cerebral embolism can usually be identified. Myocardial infarction with mural thrombosis, mitral and aortic valvular diseases usually secondary to rheumatic fever, and disorders of cardiac rhythm, especially atrial fibrillation, are usually responsible.

A cerebral embolus may have its origin in atherosclerotic plaques of the aorta and carotid arteries. Occasionally these will be dislodged during angiography. Fat, air or tumor cells may lodge in the brain as emboli. Occasionally the source of the cerebral embolism is not determined.

CEREBRAL HEMORRHAGE

Hypertensive Cerebral Hemorrhage

The clinical syndrome is usually quite definite. The patient is usually robust, plethoric and hypertensive. He suddenly develops a headache, quickly lapses into unconsciousness and has immediate and severe neurological findings, especially hemiplegia. Blood is found in the spinal fluid in approximately 75 per cent of the cases. Instability of vital signs is the usual pattern; the mortality rate is high. Survivors are usually left with severe sequelae.

The cause of hypertensive cerebral hemorrhage has been somewhat of an enigma, but most authorities now believe that hypertension is associated with arterial degeneration, especially of the perforating branches of such major vessels as the middle cerebral artery. In approximately 10 per cent of the cases the hemorrhage occurs in the cerebellum. According to Okinaka and Kameyama,[11] arterial fibrinoid necrosis was revealed to be the basic vascular change responsible for the hemorrhage in the brain. The arteries damaged by fibrinoid necrosis not infrequently formed miliary aneurysms.

The incidence of cerebral and cerebellar hemorrhages will depend upon the nature of the practice of the physician-consultant, especially whether he receives acutely ill patients, as in a city hospital, or whether he conducts a distant referral type of practice. An incidence of cerebral or cerebellar hemorrhages was listed as 13 per cent in the series reported by McKissock et al.,[12] whereas the incidence in the series reported by Aring and Merritt[8] was 47 per cent.

There are a number of other causes of intracranial hemorrhage, such as blood dyscrasias, anticoagulant therapy and tumors. The intracerebral complications of arteriovenous malformations and intracranial aneurysms will be discussed later.

Nontraumatic Subarachnoid Hemorrhage

This subject is a matter of increasing interest and concern to neurosurgeons and neurologists. Many articles have been written, but controlled studies are difficult to pursue. McKissock and colleagues have approached the problem of subarachnoid hemorrhage according to a randomized study. A Cooperative Study on Intracranial Aneurysms and Subarachnoid Hemorrhage is in progress in the United States and includes several foreign clinics.[13]

In a large series of 2116 cases of subarachnoid hemorrhage reported by McKissock et al.[14] arterial aneurysms accounted for 1183, or 56 per cent. Angiomas were responsible for 183, or 9 per cent, and no lesion was seen by angiography in 472, or 22 per cent. The additional 13 per cent were accounted for by cerebral or cerebellar hemorrhages (see preceding subsection).

The majority of the aneurysms of the circle of Willis are located on the anterior portion of the circle. They tend to appear most frequently in the anterior cerebral-anterior communicating area, at the junction of the posterior communicating and the internal carotid artery, or at the first major branching of the middle cerebral artery. The remainder of the aneurysms are found in the posterior fossa (15 per cent) or rarely on the distal portions of the anterior or posterior cerebral arteries.

The clinical picture of rupture of an intracranial aneurysm is now well known. The patient suddenly develops a severe headache, followed by vomiting, stiffness of the neck and variable degrees of prostration. Localizing signs usually do not appear early unless the third nerve is implicated. The appearance of hemiplegia, aphasia and hemianopsia usually indicates an intracerebral extension of the hemorrhage or the occlusion of a vessel distal to the aneurysm. A spinal puncture during the acute stage reveals uniformly bloody spinal fluid. Later, the fluid becomes xanthochromic.

Vascular Malformations

These are best described under the heading of arteriovenous malformations (Pool).[15] They present in several different ways, usually as seizures or subarachnoid hemorrhage. The seizures are likely to be focal or jacksonian at first, but often become generalized. Hemorrhage may be either subarachnoid, intracerebral, or both. The malformation may enlarge with the passage of time and destroy surrounding brain tissue. Because of the large amount of blood demanded by the arteriovenous malformation, other portions of the brain may suffer from a chronic degree of ischemia. Other symptoms include headache and focal manifestations such as hemiplegia, hemianopsia and aphasia.

Other Causes

Subarachnoid hemorrhage may be produced by other diseases such as blood dyscrasias, venous thrombosis, brain tumor and certain infections such as malaria.

Cause Undetermined

The number of instances of subarachnoid hemorrhage reported as "cause undetermined" is larger than might be expected. This group comprises approximately 22 per cent of the cases of nontraumatic subarachnoid hemorrhage. The onset is similar to that resulting from a ruptured aneurysm. There are no focal signs on neurological examination.

"Total" angiography reveals no aneurysm. The best explanation for this series of events is the rupture of a pial vessel. One often finds this disorder as an accompaniment of hypertensive vascular disease. It is possible that the same pathological process, namely, fibrinoid necrosis of the vessel wall, occurs; the blood is extravasated into the subarachnoid space instead of the brain.

DIAGNOSTIC TESTS

It is essential to re-emphasize the importance of a complete history, careful medical and neurological examinations, urinalysis, complete blood count and other necessary procedures, such as determination of the blood glucose value, the cholesterol value, an electrocardiogram and roentgenograms of the skull and chest. Occasionally the electroencephalogram will provide additional data.

The following additional diagnostic aids will often be of value:[16]

Palpation of the Carotid Arteries in the Neck

Stenosis or occlusion of the common carotid or external carotid arteries may be identified without difficulty. Alterations in the flow through the internal carotid artery may be difficult or impossible to determine by this method.

Auscultation

Auscultation over each carotid artery, listening for bruits particularly at the bifurcation of the common carotid artery. The presence of a bruit would suggest a partial arterial occlusion.

Blood Pressure

Determination of blood pressure in *both* arms. This is especially important if occlusion of a subclavian artery is suspected.

Ophthalmodynamometry

A pronounced drop in retinal blood pressure on the side of a suspected lesion often provides valuable information.

Examination of the Spinal Fluid

An important matter is the spinal fluid examination. It is through constant repetition and re-emphasis that the significance of a carefully performed spinal fluid examination will be appreciated fully. Spinal fluid which contains no gross or microscopic blood is important in a negative sense. In the patient with a cerebral vascular episode, clear spinal fluid is suggestive of an ischemic disorder; it does not entirely exclude an intracerebral hematoma.

"Bloody spinal fluid" means that the blood was present in the spinal fluid before the spinal puncture. It is imperative to have a precise diagnosis. One of the quickest and most reliable methods is to withdraw four tubes of spinal fluid. In cases of subarachnoid hemorrhage the contents of the tubes will be uniformly bloody. In other words, the fourth tube will appear as bloody as the first. In the case of a "traumatic tap" there will be progressive clearing of the spinal fluid. If the puncture is performed several days after the subarachnoid hemorrhage the supernatant fluid will be xanthochromic.

Cerebral Angiography

Cerebral angiography, although originally used mainly for the diagnosis and localization of brain tumors, has opened the door to a more precise understanding of the anatomic basis for various neurologic syndromes classified as "strokes," "intermittent insufficiency syndromes" and "cerebrovascular accidents." With the wealth of experience gained over the past decade, we have advanced to a stage where we can now define more exactly the indications for angiography, its limitations, and the price we must pay in terms of complications and occasional catastrophies for the information it is likely to yield.

There is no substitute for the careful clinical evaluation of the patient. Only after such a survey will it be possible to outline the proper diagnostic procedures to be carried out. The clinical differentiation of cerebral thrombosis, hemorrhage and embolism can frequently be made if a reliable history is available and if the results of the neurological examination and the spinal fluid examination are evaluated carefully.

The indiscriminate use of angiography is to be discouraged. Angiography should not be performed as a routine procedure. The main reason for caution is the fact that, even when performed with skill, this procedure carries a significant risk of complication and death.

A discussion of the techniques of angiography is not the primary function of this paper. Various methods can be utilized, depending upon the indications and the areas of major interest. These methods include: (1) injection of the common carotid artery after a percutaneous puncture (Meyer),[17] (2) injection of the vertebral artery after percutaneous puncture, (3) intravenous carotid-vertebral arteriography, (4) combined carotid-vertebral arteriography after puncture of the subclavian artery (Baker),[18] (5) percutaneous transbrachial arteriography, using a polyethylene catheter inserted by the method described by Seldinger,[19] and (6) selective catheterization of the brachiocephalic arteries, using the Seldinger technique of percutaneous femoral artery puncture.

Statistics on complications vary from one clinic to another. Lindner et al.[20] reported a complication rate of 2.4 per cent, an admirable record. Meyer[17] reported that in 84 cases of cerebrovascular disease in which both carotid and both vertebral arteries have been visualized, the incidence of complications was reduced to 4 per cent. Unfortunately, this low incidence of complications is not experienced in other areas. It may run as high as 7 per cent. The dangers of angiography increase with the age of the patient. Cerebral infarction or embolism may be precipitated where none existed before; or the symptoms from a preexisting lesion may be accentuated by angiography. Reactions to the dye may be mild or severe. Hypotensive crises may follow the injection. Angiography may be followed by focal or generalized convulsions. Postarteriographic bleeding at the site of the puncture may result in tracheal obstruction and may necessitate surgical intervention. Complications following general anesthesia may occasionally appear.

It is well to realize that cerebral angiograms of diagnostic quality cannot be produced with the ease of plain roentgenograms of the skull. The dye must be delivered in sufficient concentration to produce pictures of good quality. Either multiple injections must be made, or the films must be taken in rapid succession after a single injection. In the first instance the exposure must be made at the proper instant to insure the visualization of that portion of the vascular tree of interest to the operator. Technical difficulties in this respect may preclude films of good quality. Thus, multiple views are essential to accurate delineation and localization of a lesion.

It should be remembered that angiography demonstrates the *large* vessels of the brain. Many strokes are produced by hemorrhage or occlusion of the penetrating vessels to the interior of the brain. These vessels are usually too small to visualize in the arteriogram. Furthermore, lesions in other "remote" areas such as the cerebellum, superior portion of the brain stem, occipital lobes and possibly the tips of the frontal lobes may not distort the vascular pattern enough to be identifiable.

Angiography has a definite place in the differential diagnosis of cerebrovascular disease from other conditions. Especially when the history is uncertain and the findings are meagre or equivocal, angiography may prove very useful in differentiating intracranial and extracranial vascular disease and in identifying other surgically amenable lesions such as brain abscess, subdural hematoma and brain tumor. Every clinician of experience has encountered subdural hematomas and brain tumors with remarkable enough intermittency or abruptness of symptomatology to have suggested a vascular insufficiency episode. Indeed, the vascular changes within a glioblastoma multiforme will predispose to the development of such a syndrome. Angiography and possibly other necessary diagnostic measures should be performed promptly if there is a suspicion that the intracranial lesion is other than vascular.

If the clinical picture is that of vascular disease, one must try to ascertain what information, if any, might be derived from angiography. Generally, several categories emerge from the clinical findings and spinal fluid examination:

Occlusive Cerebrovascular Disease. *Occlusive Disease Secondary to Narrowing of Atherosclerotic Vessels.* A great deal of interest and activity are presently directed to this condition. Because we do not presently possess means of measuring the simultaneous blood flow through the large vessels of the neck, we cannot correlate accurately the relationship of many vascular kinks and constrictions with the clinical manifestations:

1. Intermittent insufficiency syndromes, carotid and vertebral. These are usually definite clinical syndromes of vascular insufficiency, not always correlated with the angiographic findings, even though the survey includes the visualization of the large vessels which emerge from the aortic arch. In the selection of cases for arteriography, those patients having lesions of the common carotid artery, carotid bifurcation and internal carotid artery in the neck would seem to deserve the most attention. Transient monocular blindness, reduced retinal blood pressure by ophthalmodynamometry, identification of bruits in the neck and the demonstration of diminished pulses by palpation may be useful clinical findings. Carotid angiography should be performed with the expectation that a stenotic or occlusive lesion can be demonstrated and removed surgically and that the symptoms for which the operation is performed will be relieved.

2. Progressing ischemic lesion. If the lesion involves the carotid system in the neck, a number of the clinical signs mentioned in the preceding paragraph will be present initially. The decision must be made to perform angiography at once and to remove the obstruction as soon as possible. A delay longer than three to four hours usually means irreparable damage to the brain. Angiography and surgery are usually not of value after this time.

3. Completed ischemic lesion. The patient with a completed occlusive episode does not ordinarily benefit from an angiographic examination. Infarction of the brain has taken place, and restitution of the circulation will not repair the brain damage.

Cerebral Embolism. The sudden onset of an ischemic vascular episode in the presence of atrial fibrillation, myocardial infarction, valvular disease of the heart or bacteremia usually provides the clinical background for the diagnosis of cerebral embolism. Angiography is seldom indicated or useful, except in those rare instances in which a large embolus lodges in areas such as the bifurcation of the common carotid artery. Angiography would be indicated at once under those circumstances, in preparation for surgical removal of the clot.

Nontraumatic Subarachnoid Hemorrhage. The immediate decision hinges upon whether the patient will survive the initial insult. If it is evident that death is imminent, as indicated by a severe depression of the state of responsiveness of the patient plus profound alterations in the temperature, respiratory rate, pulse rate and blood pressure, or if the patient's condition is so precarious as to preclude the rigors of operative treatment, angiography is a futile gesture and should not be performed as an emergency procedure. Nothing will be gained by subjecting the moribund, stertorous patient to additional trauma. However, if the condition of the patient improves and there is reasonable expectancy of survival, then a second problem emerges: the differentiation of subarachnoid hemorrhage from hypertensive intracerebral hemorrhage. Admittedly, this is not a simple matter, but the age of the patient, the history of hypertension and the early development of focal neurological signs such as hemiplegia, hemianesthesia, hemianopsia or aphasia would point to hypertensive intracerebral hemorrhage. At the present time there is no evidence that early surgical therapy directed toward evacuation of an intracerebral clot alters favorably the ultimate outcome of such patients. If the condition of such a patient stabilizes, surgical evacuation of the clot may be considered. Angiography would be indicated as a preliminary diagnostic procedure.

If the clinical findings point to the probability of a ruptured aneurysm of the circle of Willis, angiography should be done without delay. Usually the common carotid arteries are injected first. The importance of vertebral angiography is being realized, so the screening procedure becomes one of "total" angiography. If an aneurysm is present there is a good chance of its being visualized by this means. Multiple aneurysms will be identified in about 15 per cent of those patients found to have intracranial aneurysms. Sometimes an aneurysm will not fill but can be visualized at the time of a subsequent angiographic survey. Once identified, the aneurysm can be dealt with according to the best available surgical or medical therapy. The angiographic examination may reveal a vascular malformation. The decision must then be made whether to approach such a lesion surgically. In approximately 35 per cent of cases of nontraumatic subarachnoid hemorrhage the cause of the bleeding will not be an aneurysm or arteriovenous malformation. If hypertensive cerebral hemorrhage can be excluded, such patients usually have a better outlook than those with identifiable aneurysms or arteriovenous malformations.

THERAPY

General Supportive Measures

The general treatment of the patient with a severe stroke has been reviewed (Sahs).[1] The main objective is to save the life of the patient by providing adequate symptomatic and supportive measures.

Maintenance of an adequate airway, preservation of fluid and electrolyte balance, frequent turning, care of the bladder and bowels and the scrupulous avoidance of decubiti are a few of the measures which must be employed to tide the patient over the critical period. Attention must be paid to extracerebral factors which might be responsible for a fall in blood pressure in those patients who have occlusive disease. These include a survey of the previous therapeutic regimen to assess the possible role of antihypertensive drugs. Cardiac irregularities should be corrected, if possible. Anemia, if present, should be treated promptly.

Rehabilitative measures should be begun early and should be directed at first toward the avoidance of contractures which sometimes develop with surprising rapidity.

Special Considerations

OCCLUSIVE DISEASE. 1. *Anticoagulants.* The use of anticoagulants for ischemic cerebrovascular disease is probably on the decline, principally as a result of the reports of two cooperative studies, one sponsored by the Veterans Administration[21] and another by the United States Public Health Service.[10] There may still be a place for anticoagulant therapy in intermittent insufficiency of the vertebral-basilar system. The chief objections to the use of anticoagulants are the difficulties in control and the significant incidence of hemorrhagic complications.

2. *Fibrinolysin Therapy.*[22, 23] This type of therapy has not been developed to the point where adequate evaluation can be made. The incidence of pyrogenic reactions is relatively high.

3. *Surgery of the Vessels Emerging from the Aortic Arch.* Surgical procedures directed to the neck vessels has received major attention in recent years.[4, 24] The results of surgical therapy must be considered in the light of the natural history of occlusive disease.[25] Careful controls are necessary in order that the end-results of surgical therapy can be evaluated properly.

HEMORRHAGE. 1. *Surgical Therapy of Intracerebral Hemorrhage.* Intracerebral hemorrhage carries a high mortality whether operative treatment is carried out or not (McKissock et al.).[12]

2. *Arteriovenous Malformations of the Cerebral Hemispheres.* Pool[15] feels that the risk of serious consequences in patients not operated upon is approximately 40 per cent, and that it is reduced to 24 per cent if surgical excision is done. In a previous study, Svien and colleagues[26] reported among 23 patients who received no definitive surgical therapy a mortality rate of 8.7 per cent. Certainly, if the lesion is distant from the speech or motor area, preferably in the nondominant hemisphere, an attempt at removal is justifiable. Otherwise treatment of the convulsions should be handled medically.

3. *Intracranial Aneurysms.* Selected aneurysms of the internal carotid-posterior communicating junction, the middle cerebral bifurcation and the anterior cerebral-anterior communicating region can be attacked surgically. The results of surgical treatment of the first two types have been published in the reports of McKissock, Richardson and Walsh,[27, 28] and of the anterior communicating aneurysms in those of Lang and Poppen[29] and of Pool.[30]

Patients not eligible for surgery, those moribund, those with severe complicating diseases, patients with multiple aneurysms and those with inaccessible aneurysms should be managed with controlled bed rest or with hypotensive drugs. Certainly the latter type of treatment, advocated by Slosberg[31] and by Meyer and Bauer,[32] should be given more adequate clinical trials. Hypotensive medical treatment is advisable in the acute stages of spontaneous subarachnoid hemorrhages, especially if the blood pressure is elevated. Selection of cases for surgical therapy can then be assessed after further studies have been completed.

Although hypothermia has been used in the therapy of cerebrovascular lesions, the results are not outstanding to date.[33, 34] Prolonged hypothermia is a difficult undertaking which apparently carries a formidable list of complications.

CONCLUSIONS

There is no doubt about the increased interest in the subject of cerebrovascular disease. The use of angiography has given us useful information relative to occlusive and hemorrhagic disorders. Yet we do not have precise methods for measuring blood flow through a selective area of the brain, although techniques for measuring general cerebral blood flow are available.[35] We have no medical means at this time for controlling the advance of atherosclerotic processes in the neck and brain vessels although surgery to the neck vessels is presently in vogue. Far from making a significant reduction in mortality and morbidity from cerebrovascular disease, we have merely scratched the surface. More work needs to be done.

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Problems in the Diagnosis and Treatment of Myasthenia Gravis

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MYASTHENIA GRAVIS is essentially a disease of rapid pathological exhaustion of voluntary muscles with use and a slow, pathologically long period of recovery with rest. It must be clearly differentiated from the normal fatigue process of excessive use of voluntary muscles, in which the recovery period with rest is brief and efficient. No other condition of muscle dysfunction includes both this rapid exhaustion and this prolonged time of recovery. For example, the normal healthy person can chop wood vigorously for 10 minutes and then become tired, and he is forced to rest. But the rest period of 1 or 2 minutes is sufficient to restore his muscles to such an extent that he can resume the vigorous activity again. In general, the period of vigorous action is 4 to 6 times longer than the required period of recovery and rest. One of the chief muscles involved in myasthenia gravis is the levator muscle of the eyelids. The normal person can keep his lid elevated for a period of between 4 and 6 seconds. Then there is a very brief rest period during the involuntary blink of the eye which relieves this particular muscle of its sustaining requirements for a matter of only a quarter of a second. The ordinary spontaneous blink occurs approximately 15 times a minute. The myasthenic muscle, on the contrary, would require a period of complete rest of 5 to 8 seconds in order to allow the muscle to hold the eye open for a brief period of 1 to 2 seconds. This reversal of the ordinary action and rest intervals characteristic of myasthenia gravis is illustrated diagrammatically in Figure 1.

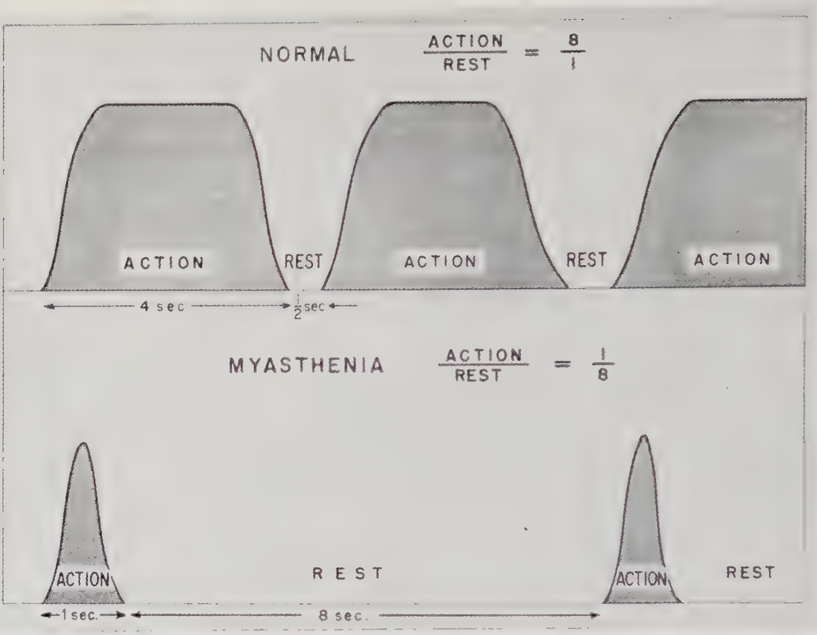

Fig. 1. Diagrammatic contrast of the normal work-rest ratio and that of the myasthenic patient.

INCIDENCE

There are no accurate figures indicating the exact number of patients with myasthenia gravis in any population group. Estimates vary from 1 in 5000 to 1 in 40,000, a spread of 8 to 1. We made a count of the living patients in the Commonwealth of Massachusetts in our clinic population, which has a total of 600 patients, in early 1962, and found 320 patients. By assuming that 80 per cent of all known patients in Massachusetts ultimately were seen by our group, and further assuming that for every known patient there is one patient unrecognized and undiagnosed, we would estimate an incidence of 1 in 10,000 patients, half known and half unrecognized, which would give the presumed number in the United States as 20,000. Admitting that these assumptions are only approximate, it is still evident that the disease is comparatively rare.

PROBLEMS IN DIAGNOSIS

The recognition of myasthenia gravis in the practice of internal medicine and neurology requires a high suspicion of the presence of the disease and a clear understanding of what the clinical presenting symptoms usually are.[4] One must look for apparent muscular paralyses or exhaustion that are transient and variable, considerable reduction of the impairment with adequate periods of rest and exacerbation of the symptoms with ordinary voluntary use. Fixed and permanent palsies do not have this characteristic of myasthenia. In myasthenia there may be an asymmetrical involvement of the ocular muscles with extreme ptosis of one eye and none of the other. A few weeks later the situation may be reversed. In three quarters of myasthenia patients the disease begins with involvement of one or the other of the ocular muscles, so that, of course, many of the early cases are seen by ophthalmologists.

A characteristic finding in myasthenia is an increase of the symptoms as the day wears on, which is the opposite, usually, of the so-called neurotic fatigue states. Since in healthy humans the peripheral and back muscles have an extraordinary amount of reserve power and endurance, mild involvement of these muscles in early myasthenia gravis is sometimes difficult to obtain in the ordinary history. For example, a 50-year-old man who had a single eye involved for a few months with ptosis complained that his bowling, which previously had included three or four games in an evening without fatigue, was now limited to one complete game.

Involvement of the bulbar muscles concerned with swallowing and talking is usually easier to identify. Speech, after a few seconds, becomes nasal in quality, a characteristic of myasthenia gravis. Clear enunciation at the level of a whisper or examples of hoarseness are not found in this condition. The dysphagia usually involves the nasal regurgitation of liquids and is accompanied nearly always by extreme exhaustion of the power of chewing, so that food sometimes has to be removed by the fingers from the mouth because it cannot be broken into small enough particles to attempt a swallow.

In 80 per cent of cases, careful attention to the history of the development of the disorder is strongly suggestive of myasthenia and separates it from the other conditions of muscular weakness. A most reliable clinical test requiring no apparatus or undue effort on the part of the examiner consists of asking the patient to look up at the extended finger of the examiner for a period of 1 minute. The patient is instructed to avoid blinking. A normal person can maintain his eyes in such an elevated manner for a minute without any ptosis being demonstrated. Untreated myasthenia gravis with early ocular involvement shows at the end of 30 seconds a tendency of one or the other of the lids to droop, and by 45 seconds usually the lid has dropped down to the pupil. By the end of 1 minute very clear ptosis is evident. Timing of this simple test gives one a rapid and reliable method of following the progress of the disease under the various forms of treatment which will be discussed later.

Voluntary ergographic tests of exhaustion of the voluntary muscles in the hand, for example, give specific pictures and characteristic curves of myasthenia gravis, but the examining internist or neurologist seldom has appropriate equipment available. Any repetitive motor action that

ORAL PREPARATIONS

Generic Name	Trade Name	Strength
Neostigmine bromide	Prostigmin (Roche)	15 mg. tablet, white, scored
Pyridostigmine bromide	Mestinon (Roche)	60 mg. tablet, white, double scored
Pyridostigmine, sustained release	Mestinon Timespan (Roche)	180 mg. tablet, scored
Pyridostigmine syrup (probably available 1964)	Mestinon Syrup (Roche)	60 mg. = 5 c.c.
Ambenonium chloride	Mytelase (Winthrop)	10 and 25 mg. scored tablets

PARENTERAL PREPARATIONS

Neostigmine methyl sulfate	Prostigmin (Roche)	Ampoules, ½ mg. per cc., 1 mg. per cc.
Edrophonium chloride	Tensilon (Roche)	Ampoules, 10 mg. per cc.
Pralidoxime chloride	Protopam (Campbell)	Ampoules, 1 gram powder for 10 cc. distilled water

normal persons do without fatigue can be used as a test for a suspected patient with myasthenia gravis, such as raising a book above his head a number of times, climbing up and down from a step, or reading aloud at a rapid rate.

The use of anticholinesterase drugs, intramuscular neostigmine (Prostigmin) or intravenous edrophonium (Tensilon), to confirm the diagnosis is highly recommended before any treatment is instituted. The textbook by Osserman covers this in more detail.[2] The accompanying table identifies both generic and trade names of the preparations available.

The specific alleviation of muscular weakness or paralysis following the administration of one of these drugs occurs only in myasthenia gravis, and, therefore great reliability is assumed in the use of such substances. With care this type of drug test gives clear-cut diagnostic confirmation in 85 or 90 per cent of such situations. However, some false positive results are encountered from time to time, and these must be kept in mind. If there is complete ptosis, for example, of the right eye, and 4 minutes after the intravenous injection of 10 milligrams of edrophonium the eye can be fully elevated and maintained without fatigue for a full minute, there is no question of the positive response. If, however, the ptosis is not very clear and after 1 minute of elevation the lid droops only 15 or 20 per cent of the maximum fall and can be elevated by a willful determined act on the part of the patient, the response to the drug may not be so clear. Usually a repeat test on a subsequent day or greater efforts at quantitation will resolve the difficulty and eliminate the false positive reaction which may involve placing the patient on a treatment schedule of drugs that he does not need.

A patient who has bulbar involvement from early amyotrophic lateral sclerosis with marked difficulty in swallowing solid food may show unexpected improvement from 10 milligrams of intravenous edrophonium or 1.5 milligrams of intramuscular neostigmine methyl sulfate that results entirely from the excess of mucous and saliva that this parasympathetic drug produces, lubricating the solid food so that it goes down apparently more easily than before. If he keeps in mind that there are false positives reactions, the alert clinician can usually suspect and identify them by repeating the test.

Highly suggestible patients with neurotic fatigue will improve their motor performance after the administration of any drug parenterally. A simple method of identifying such hypersuggestibility involves the intramuscular injection of 0.6 milligram of atropine sulfate prior to the administration of the intramuscular neostigmine or the intravenous edrophonium. The atropine prevents the side effects of the anticholinesterase drugs on the gastrointestinal tract, which is desirable in most instances anyway, and serves as a placebo control for the anticholinesterase preparation. The myasthenia patient, obviously, will show no benefit from the atropine, whereas the suggestible patient will. We consider the use of atropine in this manner far better than a complete placebo injection of normal saline because there is no anticholinesterase effect of the atropine and the patient is looking for something of this sort. It also has a very specific preventive value, as stated, in reducing the undesirable muscarinic side effects of the anticholinesterase medication.

Finally, if one is not completely sure of the parenteral confirmation of the disease by the use of these drugs, it may be useful to try, for a brief period only, for example a week, the oral use of tablets of neostigmine bromide. Placebo tablets, of course, could be used on alternate days and a very careful subjective and objective evaluation of the patient obtained. However, this is very seldom necessary. Unless he is highly suggestible, a patient who does not have myasthenia gravis will report little benefit, if any, from oral tablets, whereas the myasthenic patient will find that many of his symptoms are much better on the oral medication, and when he comes in for a check up this will be shown objectively to the examining physician.

It is said that the myasthenia patient, because his disease involves some lack of a chemical in his system, can tolerate much larger doses of anticholinesterase drugs than the normal person. This has never been fully demonstrated, although there is strong clinical impression that this is so in many situations. The myasthenia subject or the normal person can adapt himself slowly to rather large doses of these drugs. It is not unusual for a patient to appear who has been taking as many as 15 tablets of neostigmine bromide in 24 hours, and who has no evidence of side effects from this drug and no myasthenia gravis. Usually, however, doses of this level produce chronic side effects such as diarrhea, cramps and excessive salivation in the normal person, and they suggest, when they occur, that myasthenia gravis is not present.

TREATMENT

General

The myasthenia patient should have special attention at the very beginning to his general medical condition such as his state of nutrition, any chronic infections in either the pulmonary or renal systems, and of course, his emotional state. It is far more difficult to handle myasthenia gravis in the presence of other disease than it is alone.

Treatment with Anticholinesterase Drugs

In the early days of treatment by anticholinesterase drugs such as neostigmine bromide it was thought that every patient with this disorder could be balanced successfully so that all of his symptoms could be neutralized, and that he would be normal as long as he took the compound. This is far from the truth. Only about one third of the patients in our experience can be so balanced even with the most meticulous individual regulation and frequent readjustment of the medication. About one third have good alleviation of most of their symptoms so that they are 60 to 75 per cent of normal. The remaining third have only partial help so that their myasthenia gravis is still clearly in evidence even though they are taking as much medication as they can tolerate.

There are three substances available at the present time for the oral treatment of myasthenia gravis. These are neostigmine bromide, pyridostigmine bromide and ambenonium chloride. It is considered wise to begin patients on neostigmine (Prostigmin), which is more likely to have muscarinic side effects on the intestinal tract if the dosage is even slightly in excess of the patient's requirements. The identification of this overdosage, early in the treatment period, is excellent instruction to the patient and to the physician in charge. The sophisticated patients who have had this treatment for the disease for any length of time easily recognize symptoms of overdosage. Neostigmine bromide is available in a 15 milligram, white, scored tablet. Regulation of myasthenia by this drug varies tremendously from patient to patient, and even in the same patient at different times. Some patients adjust quite readily, with elimination of nearly all of their symptoms, to small doses of this drug, such as one tablet three to four times a day, equally spaced. Others require as many as three tablets (45 milligrams) every two or three hours during the waking hours, and sometimes during the night. The largest dose that we have used has been a phenomenal 121 tablets in 24 hours, but others have reported even larger doses. One of the extraordinary puzzles is how the human body can tolerate nearly 2 grams in 24 hours of such a toxic substance without serious side effects in the presence of this disease. This amount would be immediately fatal in any normal person.

The second drug is pyridostigmine bromide (Mestinon bromide), which is available in a double-scored white tablet containing 60 milligrams. One tablet of pyridostigmine is approximately equal to one tablet of neostigmine in its effectiveness in myasthenia gravis. Pyridostigmine causes less gastrointestinal stimulation than neostigmine so that it is frequently used when there is sensitivity in this regard, and the dose, therefore, can usually be increased more in such patients before side effects develop. There is some evidence, although it is not very convincing, that this form of anticholinesterase is more effective in the ocular type of myasthenia than neostigmine itself. The same problems of individualizing the dose and distributing it throughout the day exist with pyridostigmine as with neostigmine. There is some evidence that pyridostigmine has a little longer effect than neostigmine. A sustained release form of pyridostigmine (Mestinon Timespan) containing the equivalent of three tablets (180 milligrams) is available. This form of the drug is very useful to give the patient who has symptoms during the night so that he will not have to wake up to take his medication. It must be remembered that during sleep the demands of the muscular system are reduced and therefore less medication is required during this period. A patient taking two tablets of pyridostigmine at a time during the day would get along very well with only one of the sustained release tablets of 180 milligrams during the night. The sustained release form lasts approximately six to eight hours so that it should carry a patient through the night. To use it during the day requires careful spacing, with this interval of time in mind. A sustained release tablet taken in the morning about 8 o'clock should still be effective, theoretically, in the early afternoon, and one taken then would take the patient through midnight, so that it is quite possible to regulate a patient efficiently on three tablets a day of the sustained release form: one in the morning, one in the afternoon and one at bedtime. However, if one takes the sustained release form at shorter intervals there is surely going to be an accumulation of the drug which will reach its maximum during the sleeping hours and at a time when the patient's muscular demands are at a minimum. This awakens him with side effects of stimulation of the intestinal tract. Complaints of early morning diarrhea are common and severe toxic reactions of the cholinergic type will follow if this type of administration is continued. The sustained release form should not be used at intervals shorter than every six hours. For patients who have difficulty in swallowing tablets, for young children who cannot manage tablets at all, or for the postoperative patient whose swallowing is uncertain, there is a syrup of pyridostigmine (Mestinon syrup) that we hope will be available commercially in 1964. It can be made easily by any pharmacist from the tablets; the strength of the syrup should be 60 milligrams per 5 cubic centimeters. The syrup has another advantage that finer dose adjustments can be made, whereas breaking the tablets into quarters or eighths is exceedingly difficult. Occasionally patients report that the syrup of pyridostigmine is less upsetting to their intestinal tracts. This suggests that the presence of the sugar in the syrup is the important factor; usually the same results can be obtained by taking some food, a cracker or glass of milk, with the tablets.

The third drug is ambenonium chloride (Mytelase), the most recent of the anticholinesterase drugs that have been introduced. It has a double or bis-molecule and has definitely a longer effect. It comes in 10 and 25 milligram tablets. The 10 milligram size is approximately equal to a 15 milligram neostigmine bromide tablet or a 60 milligram pyridostigmine bromide tablet. It has a slightly less stimulating effect on the gastrointestinal tract than neostigmine bromide but is not quite as innocent in this regard as pyridostigmine. We recommend starting a new patient on neostigmine bromide because it has the most stimulating effect on the gastrointestinal tract. The patient should be introduced to this side effect early in his treatment so that he will be familiar with it. After this drug has been tried, and if it has not been satisfactory, either ambenonium or pyridostigmine may be used, remembering the equivalents previously mentioned.

It is very unusual that a patient cannot be adjusted to one of these three drugs with maximum reduction of his myasthenic symptoms, but occasionally the best arrangement for an individual patient is a mixture of two drugs, either taken alternately or sometimes taken together in appropriate amounts. We have had experience with only one patient who worked out a schedule of his own of all three drugs which he felt was superior to any one or any two. This sort of event is exceedingly rare and does not make a great deal of pharmacological sense.

These three compounds produce the same side effects by stimulation of the gastrointestinal tract, and if taken in amounts beyond the patient's requirements and tolerance, will produce cholinergic block of the myoneural junction. If this is continued it will produce dangerous cholinergic crises which can well terminate in death. It is obvious that when the top dosage of any one of these drugs is reached the addition of even small amounts of another drug of this type will surely produce a cholinergic toxic condition. We have encountered patients who have been at the top level of medication on one drug with perhaps only alleviation of 50 per cent of their symptoms, and the physician has therefore boldly added standard doses of one of the other compounds, only to produce a catastrophe of cholinergic crisis within several hours. The side effects are *additive* with all three of these compounds, and this fact must be kept clearly in mind in adjusting patients to combinations of these drugs.

The Regular Use of Anticholinergic Drugs (Belladonna Type)

In spite of the published warnings in the medical literature during the last eight years, some physicians follow the dangerous policy of prescribing atropine sulfate or other drugs of an anticholinergic type in addition to the antimyasthenic drugs in order to neutralize or prevent stimulation of the gastrointestinal tract. We have seen a patient recently who had been given three neostigmine bromide tablets every two hours during the day, and with each one, 0.6 milligram of atropine sulfate. Not only were the side effects of so much neostigmine completely obscured by this massive amount of atropine, but also cholinergic block was beginning to develop. In addition, this patient was also suffering from chronic atropine toxicity, was running a temperature and had a hot, flushed, dry skin, dilated pupils, some ataxia and confusion. It is good therapy, and good sense, if one dose of anticholinesterase medication produces severe stimulation of the gastrointestinal tract, to use a single injection of atropine sulfate to quiet this excessive stimulation. This is entirely different from the regular, repetitive, continuous administration of such compounds with the myasthenia medication. We have seen repeatedly patients brought into the hospital in respiratory difficulty, requiring tracheostomy and the use of a respirator, who were in a real cholinergic crisis due to the use of atropine along with antimyasthenic medication; the warning side effects were completely obscured and neither the physicians nor the patients were able to identify them. We and others believe that many of the deaths in myasthenia gravis are due to excessive use of anticholinesterase medications which have been prescribed in order to neutralize the myasthenic symptoms but which have instead produced cholinergic crises that might have been recognized and prevented if the use of atropine had been avoided. The sophisticated and properly instructed patient will identify the warning signals of too much medication and will reduce subsequent doses so that these side effects are eliminated. Since partial remissions in myasthenia gravis are common (some are spontaneous and others are induced by such procedures as x-ray therapy or thymectomy), patients should be instructed in how to handle their dosage schedule when such good fortune occurs. It is obvious that if a patient is well adjusted to a certain level of antimyasthenic medication and then goes into a partial remission, the same level of medication will now produce excessive stimulation and therefore must be reduced. All that is necessary is proper instruction and indoctrination of the patient by the physician. This situation can then be recognized and side effects properly and promptly eliminated by the correct reduction in dosage.

Crises

The chief emergency that arises in the management of moderately severe myasthenia is the differential diagnosis of the *cholinergic crisis* from that caused by an acute exacerbation of the disease (myasthenic crisis). Excessive amounts of any of the three drugs mentioned, alone or combined, that are well beyond the patient's requirements produce a muscle weakness that is just as serious a threat to the patient's life as the myasthenia itself and dangerously interferes with breathing, coughing and swallowing.

If a patient is in the overmedicated state (cholinergic crisis), and if through lack of recognition of this state more medicine is given (by injection, for example), a fatal outcome can easily and rapidly occur. Overmedication can occur when the myasthenia is lessened by x-ray treatment and the drug schedule is kept the same.

To determine whether a patient is overmedicated, look for these signs: (1) small pupils, (2) excessive saliva, (3) twitching of the muscles in tongue, lips or shoulder, (4) cramps, diarrhea, nausea, (5) excessive sweating (cold sweat), (6) difficulty breathing, coughing and swallowing.

Signs of undermedication are: (1) increase in ptosis, (2) normal or large pupils, (3) no muscle twitching, (4) weakness of jaw, inability to hold up head, (5) no cramps or diarrhea, (6) increase in nasal voice, (7) difficulty in breathing, coughing and swallowing.

Note: *Weakness of bulbar muscles is found in both conditions.*

TENSILON TEST (EDROPHONIUM TEST). This is the *only* safe drug to use. Don't, unless you are absolutely certain, inject neostigmine.

Inject 2 mg. or even 1 mg. of edrophonium into a vein.

If there is an immediate improvement in strength, voice, breathing, jaw power and grip, wait five minutes and inject 4 mg. If the improvement after the 4 mg. injection is clearer and more evident, the patient is undermedicated and requires more medicine by mouth (neostigmine, pyridostigmine or ambenonium) or an injection of neostigmine. Edrophonium will only last 10 minutes at the most.

If there is immediate worsening of symptoms of even a slight degree, or if there is no effect at all, overmedication is present. The worsening will last only a few minutes and does no harm in most instances. Use atropine intramuscularly 0.3 mg. to 0.6 mg. and, if available, 25 to 50 mg. of pralidoxime (Protopam Chloride) intravenously. Do not use more, for it would push the patient into a state of a myasthenic crisis.

In general, it is more dangerous to have overmedication than undermedication in bulbar myasthenia gravis. If respiration is seriously involved, a tracheostomy must be done, or as a temporary measure, intubation. Manual artificial respiration is life-saving until a respirator can be secured. Frequent use of suction is required until secretions are no longer a problem.

If this emergency occurs in the hospital it is difficult enough to cope with, but in a patient's home, the challenge to the attending physician is indeed momentous and failure is far more frequent than success.

X-ray Therapy

Since nearly 80 per cent of all myasthenia patients have microscopic pathologic lesions in the thymus gland it is reasonable to direct the therapy toward this organ. At the present time, we do not know how this gland is related to the production of symptoms so there are only two means of attacking the thymus. The first is radiation of the thymus to reduce it in either size or activity, and the second is to remove the gland surgically. Empirically we have found that 3000 roentgens of x-ray treatment given in 10 to 12 divided doses to the mediastinal area produces remissions that are usually only partial in approximately 50 per cent of all patients who have had this form of treatment. Sometimes the remission is very small, but the period of time between the termination of the x-ray therapy and the appearance of the remission (six to ten weeks) is sufficient to make it highly probable that x-ray treatment is affecting the disorder. Occasionally x-ray therapy produces a complete remission of the symptoms and the patient is entirely well without requiring any medication. Our experience is that this complete remission will not persist so that after 6 to 18 months the symptoms will slowly develop again and reach the same level as before the x-ray therapy was instituted. There are, however, some patients (we have only one in our series) who have had a complete remission that has persisted after an adequate amount of deep x-ray therapy to the mediastinal region. We think it wise to withhold any other form of treatment during such a complete remission until very clear evidence of the return of symptoms is at hand.

We cannot say at the present time how many courses of x-ray therapy can be given to a patient several years apart without danger, but we have given three such series to some mature adults at intervals of approximately two to three years, partial remissions occurring after each, and with no evidence of other damage caused by the treatment.

Thymectomy

There are still some who feel that thymectomy in myasthenia, when there is no evidence of a thymoma or tumor, has not proved effective. Our experience,[6] however, has been so clearly convincing in the selected patients who have had this procedure that we deem it the procedure of choice in these situations. In a series of more than 120 female patients up to the age of 40 who had the disease less than six years and who had moderate to severe involvement, removal of the thymus gland was accompanied by complete and permanent remissions in one third of the cases. We have excluded the purely ocular cases from this group. In a series of nonoperative cases, similar in size and matched roughly in severity and in sex to those operated on, the spontaneous total remission rate is only 5 per cent. Partial remission, which in many cases is very satisfactory achievement for patients since they are now nearly symptom-free on a small amount of drugs, occurs in another 30 per cent of the thymectomy cases, and in only 20 per cent of the nonoperative cases.

The results among our male patients under 40 years of age are much more uncertain, largely because of the much smaller number who have had the operation, so that the statistical comparison with the nonoperative group is not relevant. We have had some permanent remissions following the operation in young men and we feel that in any situation in which the procedure is desired it is very worth while to go ahead with it.

The situation with thymomas is still disturbing to us and puzzling. In theory, the surgically complete removal of active tumors such as thymomas should be followed by an even higher incidence of remission than when non-neoplastic glands are removed. This is, however, not true in practice. Among our male patients who have had thymomas removed surgically, even those who have had preliminary 3000 roentgens of x-ray therapy, the complete remission rate is only 1 out of 21. Only two others are still surviving with little evidence of any remission at all. The remainder have died. The female group is more encouraging. Of 23 females who have had thymomas removed, 13 are still surviving, and five of these are in complete remission. Three others are in partial remissions.

At the present time we strongly recommend thymoma removal for all females in whom such tumors have been demonstrated by x ray, but we recommend that, before the operation, 3000 roentgens of treatment be given. The patient should then be watched carefully and after three to six weeks the tumor should be removed. For males we feel that the tumors ought to be removed in spite of the poor statistics that have just been reported; here again the preliminary x-ray therapy should be given and followed, after an appropriate interval, by removal of the tumors.

The cause of the failure of thymoma remissions to occur is not at all clear. One supposes that recurrence of the tumor is the essential difficulty. Indeed, Osserman[3] reports that subsequent operations on several of his patients have revealed recurrence of the thymoma, which has been removed with some benefit.

In our own series we have reoperated on only two patients and found nothing pathologic at the second operation, although one of these patients at postmortem showed evidence of recurrence. One patient was in a complete remission for six years and then had a rapid recurrence of her myasthenia and subsequently died. A large thymic tumor had recurred in this patient and was found at the postmortem examination.

Other Surgical Procedures

In Paris, Thevenard recommended denervation of the carotid sinus bilaterally as a surgical attack on myasthenia gravis; after his death, Passouant[5] reported a remission rate of approximately 30 per cent in his series of 25 such procedures. None of these remissions were convincingly complete, however, and the procedure has not met with any success elsewhere. It carries a rather low operative risk and it is surprising that surgeons have not been more interested in trying to confirm or disprove the results of Thevenard and his surgical associates.

When there is severe dysphagia and other bulbar symptoms so that the patient has extreme difficulty in maintaining his caloric intake, let alone ingesting the frequent oral medication that such cases usually require, it is considered wise to do a gastrotomy. This was first reported in the literature by the late Harold Wolff;[1] the patient did very well with an artificial opening into his stomach and was able to feed himself without difficulty and to maintain his caloric requirements efficiently. We have done this in two cases with good results. In a third case the procedure was surely life-saving since the patient was unable to swallow any food at the time that the gastrotomy was done in another hospital. After the procedure had been completed, this woman was able to feed herself and restore some 25 pounds of weight over a period of two months. The advantages of this procedure are that the patient is freed completely of the anxiety of choking on either food or medication. The liquid feedings may be self-administered without difficulty throughout the day, and adequate intake of both fluids and calories can be maintained without trouble. Finally, it puts to complete rest the whole swallowing mechanism so that a sustained period of rest for the involved muscles may be achieved. The procedure may be done in a half hour under local anesthesia and carries a very small risk, if any, to the patient. If a remission occurs so that swallowing is again possible, the gastrotomy aperture can be surgically closed without difficulty at any time desired.

It is no problem at all to crush the tablets of the regular type or the sustained release form of pyridostigmine bromide and to administer the drug in a little milk or water by catheter through the gastrotomy opening.

CONCLUSIONS

Myasthenia gravis is a comparatively rare condition; the present evidence suggests that there are probably no more than 10,000 known cases in the United States and another 10,000 unknown cases. Treatment by drugs, using the three available anticholinesterase compounds, must be individualized carefully for each patient and continual supervision of intake and dosage schedules must be maintained at all times.

For patients not responding satisfactorily to these oral medications, x-ray therapy to the thymus region is recommended in doses of 3000 roentgens over a divided period.

For female patients under 40 years of age who still have considerable amounts of myasthenia that is not responding to treatment, removal of the thymus gland is recommended. For all those patients who show tumors in this region thymectomy should be done. For young males, the procedure is certainly one that ought to be considered, although our our own statistical data fail to show any benefit from surgery in these patients.

In spite of all these efforts at therapy, myasthenia gravis carries a mortality rate of approximately 10 per cent after a period of 10 years from onset in most of the clinics specializing in the management of this disease.

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THE STRUCTURE of the muscle cell may be roughly divided into the following areas: (1) Within the sarcoplasm glycogenolysis takes place through the Kreb's cycle. It is also within the sarcoplasm that myoglobin is found. Thus, in abnormalities affecting myoglobin and glycogenolysis down to the Kreb's cycle one may find chemical and anatomical abnormalities within the sarcoplasm. (2) The muscle cell contracts by shortening of its fibrils. The most commonly accepted theory of this, today, is the interdigitation of the I and A bands on contraction. The A band is made largely of myosin, whereas the I band is largely actin. Huxley and his colleagues have demonstrated that upon shortening of the muscle the I band interdigitates with the A band.[19] Abnormalities of the myofibrils themselves are found in nemaline myopathy,[39] in which palisades of fibrillary structures without normal cross-striations are found, and in the ringbinden found in other myopathies in which there is an abnormal dislocation of the normal myofibril.[10, 16, 47] In addition, fibrillary changes may be seen in central core disease.[41] (3) Traversing the muscle cell in a triad at the Z disc and turning also parallel with the fibrils is the endoplasmic reticulum. It is this structure which is largely responsible for the regeneration of RNA in the formation of new muscle cells, and the central part of the triad at the Z disc may be responsible, according to the work of Ruska et al.,[35] for the propagation of the action potential internally within the muscle cell. Two abnormalities associated with abnormal endoplasmic reticulum and difficulty in transmission of the action potential along the muscle cell are familial periodic paralysis and paramyotonia congenita.[42] (4) Recently attention has been drawn to a disorder with an intense hypermetabolism (BMR +200) with normal

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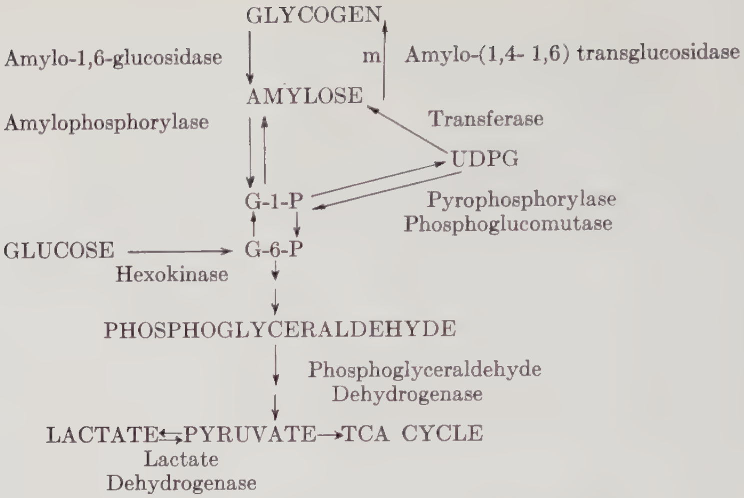
GLYCOGEN
Amylo-1,6-glucosidase
m
Amylo-(1,4- 1,6) transglucosidase
AMYLOSE
Amylophosphorylase
Transferase
UDPG
G-1-P
Pyrophosphorylase
Phosphoglucomutase
GLUCOSE
Hexokinase
G-6-P
PHOSPHOGLYCERALDEHYDE
Phosphoglyceraldehyde
Dehydrogenase
LACTATE
PYRUVATE
TCA CYCLE
Lactate
Dehydrogenase

Fig. 1. Present concept of the breakdown of glycogen.

thyroid function. Of the tissues examined to date only the muscle cells were found to have profusion of giant mitochondria, which showed three types of architectural structure and abnormal respiration.[22] (5) Muscle is a mesenchymal tissue and differentiates early in the embryology of the individual. Abnormalities in differentiation of the muscle cell are seen in myositis ossificans.

Propagation of the action potential down the muscle cell has been shown by the Hodgkin-Huxley equations[18] to be due to the sudden penetration of sodium ions within the cell. The resting potential of the cell in turn is presumably due to the amount of potassium ion. Endocrine disorders commonly dissociate such ionic equilibriums.[38] Thus, abnormalities of muscle are seen in parathyroid disease, disease of the renal tubules, disorders of the thyroid gland, Addison's disease and Cushing's disease. All the disorders listed above are essentially rare, but all give insight into the normal function of muscle. It is proposed to take up each of these disorders in turn.

DISORDERS FOUND PRIMARILY IN THE SARCOPLASM

Liver and muscle together constitute the main depots of glycogen. The present concepts of the breakdown of glycogen are illustrated in Figure 1. It is now apparent that the phosphorylase enzymes necessary for the breakdown of glycogen to glucose-1-phosphate are indeed different in different structures of the body. Thus, at least two types of phosphorylase are found in muscle (Fig. 2). Both are absent in McArdle's disease.[25] One is markedly deficient in central core disease, and neither is abnormal in the classical glycogen storage diseases. However, in both of the first of the above disorders liver phosphorylase is normal.[13, 36] In both glycogen storage disease and McArdle's disease glycogen may be stored in excess of 1 gram per 100 ml. within striated muscle. Glycogen is found both diffusely within the sarcoplasm and along the fibril in particular, according to the work of Engel,[11] along the I band of the muscle.

Two types of primary glycogen storage disease may affect muscle. The first is the cardiac form of glycogen storage disease. In 50 per cent of the patients with this form skeletal muscle is affected, the tongue receiving the greatest impact and the diaphragm the least. Unlike the classical hepatorenal form of glycogen storage disease, in which there is an absence of glucose-6-phosphatase, the enzymatic disturbance in the cardiac form has yet to be elucidated, since there is no glucose-6-phosphatase in muscle and phosphorylase in this disturbance is normal. Some investigators[21, 32] believe that in this disorder there is an excess branching and decreased chain length of the glycogen found in the muscle cell. This would make the disorder an abnormality of α 1–6 glucosidase. In such disorders an infant may frequently present as a "floppy child" with hypotonia and decreased reflexes and an enlarged heart. Sections of striated muscle in these patients demonstrate large quantities of vacuolation within the muscle cell, and the vacuoles in turn may be filled with large amounts of PAS-positive material. This material disappears upon incubation with diastase. The other form of glycogen storage disease which may affect striated muscle is a storage disease of liver and muscle. Only two cases have been reported to date.[3, 43] The Coris have postulated in this disorder a deficiency of the debranching enzyme. Once again, phosphorylase is normal in this disorder. Hence, this would be a deficiency of α 1–4 transglucosidase.

McArdle, in 1951,[25] drew attention to a new disorder of muscle in which there were frequent muscle cramps upon exertion followed by weakness, and studies of such patients demonstrated upon exertion a decrease of lactic acid and pyruvic acid instead of the usual increase seen after exercise. McArdle postulated that this was an abnormal breakdown of glycogen and thought perhaps the abnormality lay in the S—H linkage in enzymatic structures. It remained for Schmid in 1958[36] to show clearly that this was a disorder in which there was an absence

$$(1)\ 2\ \text{phosphorylase } b + 4\ \text{ATP} \xrightarrow[\substack{\text{Kinase}\\ \text{(epinephrine)}}]{\text{Mn}^{++}} \text{phosphorylase } a + 4\ \text{ADP}$$

$$(2)\ 2\ \text{phosphorylase } b + 4\ \text{Pi} \xleftarrow{\text{PR Enzyme}} \text{phosphorylase } a$$

Fig. 2. Skeletal muscle phosphorylase.

of both phosphorylase B and A in striated muscle. Schmid went further and characterized the usual clinical course of McArdle's disease, which may be seen below (Fig. 1). Since that time, Pearson[31] and Engel[12] have reported other examples of this disorder. The example of Engel[12] is of interest in that the first three stages listed above were skipped and the patient presented at the last stage. Engel's case was of even more interest in that the sibling of the patient demonstrated only 50 per cent normal phosphorylase in his muscle and had cramps but did not have the pathologic changes noted above. Engel's patient had a normal amount of glycogen, i.e., 0.9 gram per 100 ml. Schmid's patient, however, had an abnormal deposition of glycogen within the striated muscle. In addition, architectural changes within muscle fibers may be seen and there may be seen intense endomysial reaction to this primary enzymatic disorder of muscle.

In 1956 another new disorder of muscle with a characteristic pathognomonic abnormality was described in children in which a central core of abnormal fibrils was noted and in which no mitochondria or endoplasmic reticulum was noted.[13, 37, 40, 41] This was originally described over three generations of the same family. It does not, apparently, shorten the life span of the patients. Such patients present with a proximal weakness and preserved reflexes. The disorder is extremely slowly progressive or demonstrates no progression whatever. Mahler,[13] in the study of such a family in England, demonstrated again an abnormality of phosphorylase within an affected patient and within the nonaffected father of such a patient. Here the abnormality was limited to phosphorylase A; phosphorylase B was apparently normal in that cytochemical studies demonstrated that the addition of AMP and manganese would give normal phosphorylase stain except within the central core portion of such fibers. Here again glycogen is not stored. The absence of storage of glycogen in such disorders suggests that the alternate cycle more recently elucidated is utilized in both of the latter two disorders. This is the UDPG (uridine di-phosphate-glucose) cycle.

Aside from these four abnormalities of carbohydrate metabolism of muscle, there has long been recognized the relatively rapid paralysis associated with massive destruction of the muscle cells and release of myoglobin. This has been termed paroxysmal myoglobinuria. Although myoglobin may be released in such disorders as McArdle's disease in its acute phase or in crushing lesions to muscle, paroxysmal myoglobinuria is a spontaneous disorder followed usually by intense paralysis of striated muscle and precipitated by either infection or trauma. The myoglobin in the urine may be demonstrated by a benzidine test and an absence of red cells within the urine with a relatively clear plasma. This is true because of the lowered threshold of the kidney to the low molecular weight of myoglobin, the threshold being about 20 mg. per 100 cc. If the patient survives the attack of myoglobinuria and the intense paresis with absence of reflexes, a biopsy of striated muscle in approximately nine days shows intense numbers of basophilic fibers in which are found characteristic large vesicular nuclei with prominent nucleoli. Early cross-striated fibrils may be seen within such muscle fibers. Such fibers may constitute 50 per cent or more of the population sample. It is this disorder which demonstrates above all others that such blue fibers are indeed regenerating muscle cells in that the patient may entirely recover in a period of a few months, even though he has a massive destruction of over 60 per cent of his muscle mass. It is in this disorder that the possibility of a molecular abnormality of myoglobin exists much like that of hemoglobin in a hemoglobinopathy. Future studies using chromatographic techniques and electrophoresis (fingerprinting)[20] plus amino acid sequence studies would be of extreme value.

MYOFIBRILLARY ABNORMALITIES OF MUSCLE

Within the past year another congenital nonprogressive myopathy has been described in a 4-year-old child who presented as a "floppy infant" with proximal weakness of the extremities and no involvement of muscles innervated by the cranial nerves except the sternocleidomastoids.[39] There appeared to be involvement of a sibling and weakness of the proximal muscles of the mother, but no pathologic evidence of myopathy was seen on biopsy section of the mother. Examination of the involved muscles of this child also showed a peculiar anatomical abnormality in which 40 per cent of the medium-sized fibers had within the muscle cells small rods which frequently occupied half to all of the muscle cell and were frequently found in palisades at right angles to the plane of the normal fibrils. Abnormal nuclei which were vesicular with prominent nucleoli were also seen within the affected fibers. Although the rodlike forms were of the diameter of normal fibrils, they did not show any normal cross-striations. They were also ATPase-negative and did not polarize or take up fluorescent antibodies to heterogenous antimyosin or antitropomyosin. Electronmicroscopic examination of biopsied material showed such rods to be of fibrous material with a periodicity of 145Å. On fixed sections, the rods stained as normal fibrils with HVG, H & E and Gomori trichrome stains and were not connective tissue. Between such rods were fine filaments with the same periodicity which did show some ATPase staining and fluorescence. It could not be ascertained whether the rodlike palisades represented separate discrete entities or part of a coil. The disorder was therefore termed "nemaline myopathy."

Another fibrillary abnormality seen in many myopathies but in particular in dystrophia myotonica is the ringbinden, first described by Heidenhain in 1918[17] and subsequently by Wohlfart[47] and Greenfield et al.[16] among others.

The ring fibril is found always within the sarcolemma and may traverse at right angles the normal fibrils. Thus, the muscle fibers may be ringed by abnormal fibrils or such fibrils may be eccentric within the fiber or may penetrate through the fiber forming a figure eight. That such fibrils are not artefacts can be demonstrated by their not infrequent internal location and by the fact that the sarcolemmal nuclei leave their normal axis, parallel to the fibrils of the fiber, and rotate to follow the ring at right angles. Cytochemical studies of ring fibrils show them to be of the same structure as normal fibrils but merely disoriented in the axis of their plane.[10] They may be found normally with aging or in the extraocular muscles. They commonly spiral and hence no beginning or end is usually seen on cross-section of the fiber.

In addition to the chemical difference in glycogen metabolism noted previously in central core disease, a fibrillary abnormality is also noted. The fibrils in the core are closely packed without mitochondria or endoplasmic reticulum between them. In addition, the sarcomere distance may be less in the fibrils in the core. Of more interest is the dislocation of the Z disc at discrete areas within some cores so that they may even become parallel with the plane of the fibrils instead of transecting them.

DISORDERS OF THE SARCOLEMMA AND ENDOPLASMIC RETICULUM

Two spontaneous paralytic diseases occurring without apparent cause are known to date. These are familial periodic paralysis and paramyotonia congenita. In the first of these disorders there is a low potassium in the serum in the majority of attacks. In the second there is a high potassium in the serum in the majority of attacks. Each disorder is characterized by recurrent attacks of flaccid skeletal muscle paralysis associated usually with an absence of deep tendon reflexes. In the hypokalemic variety it is of interest that the muscle may not be excited either directly or indirectly, and with indwelling microelectrodes no action potential may be seen propagated down the sarcolemma. The majority of patients with familial periodic paralysis demonstrate a pattern of dominant inheritance. There is no direct relationship between the amount of hypokalemia during an attack and the degree of the weakness. Attacks may be brought on by rest or ingestion of large amounts of carbohydrates, by epinephrine or by insulin. The majority of attacks occur during the sleeping hours and usually the patient awakens early in the morning with complete quadriparesis. Fortunately, most of the cranial musculature is spared. There may, however, be severe cardiac dysrhythmias with the attack. There is always an associated oliguria or complete anuria. Thus, the patient is in positive potassium and sodium balance at the time of the attack.

In the second disorder, paramyotonia congenita, once again there is an imperfect correlation between the time of the attack and the level of potassium in the peripheral serum. In this disorder, myotonia may usually be elicited from the lingual musculature. It is of interest that the myotonia may be precipitated more by cold, and myotonia in the extraocular muscles leads to a characteristic lid lag. Between attacks the patient is usually normal aside from the myotonia. At the time of attack the patient shows no myotonia and has a flaccid paralysis with loss of reflexes and sparing of bulbar musculature. In this disorder, attacks may frequently be averted by the giving of carbohydrate. Intracellular studies have not been carried out completely, and it is not known whether the action potential may be propagated along the sarcoplasm or endoplasmic reticulum during the paretic stage.

It is of interest that in both of these disorders an accumulation of fluid may occur within the muscle fiber. Such fluid is usually loculated and electronmicroscopic studies have demonstrated that most such fluid lies within the endoplasmic reticulum. Mitochondrial aberrations have also been seen during an attack of familial periodic paralysis. Within these fluid loculations granules may be seen which appear to be periodic-acid-Schiff positive. In familial periodic paralysis glucosteroids such as triamcinalone will readily precipitate an attack. No abnormality of aldosterone has been detected in studies to date; however, it has been suggested by some investigators. Measurement of excreted aldosterone by double isotope derivative methods, the giving of aldosterone to precipitate an attack or the changing of the plasma volume are all without effect in familial periodic paralysis. In this disorder intracellular microelectrodes have demonstrated that the resting potential is within the same standard deviation as that of normal muscle. The same has been shown recently by Norris[30] in paramyotonia congenita. Within the past few years Gamstorp[15] has reported a large pedigree in the Scandinavian countries of hyperkalemic paralysis without myotonia. In the United States, others have shown myotonia with the attacks[7] and between attacks, and in England McArdle[24] has demonstrated the same. Radioactive isotopic studies demonstrate that potassium does not reach an equilibrium between the muscle cell and plasma as in the normal person. It would appear that in familial periodic paralysis, at least, the potassium aberration is secondary to carbohydrate abnormality, and that it is not the primary cause of the disorder in that one may have severe paralysis with normal potassium, or one may have hypokalemia without paralysis.[42] Both disorders are transmitted as a single autosomal dominant. Not so easily explained are two more recent cases of familial periodic paralysis in which the characteristic loculations of fluid were not seen at the height of paralysis. In these patients, however, the resting potential was within normal limits. Obviously the treatment regimens in the two disorders are diametrically opposite. In familial periodic paralysis carbohydrate should be withheld, particularly in the evening hours. Potassium may have a prophylactic effect against attacks. In paramyotonia congenita potassium is contraindicated and carbohydrates may be given to prevent attacks. It is obvious that the two should be clearly differentiated before treatment is initiated. Other than the thenar myotonia and lingual myotonia the presence of a lid lag should be sought for in every case of episodic paralysis. The fact that an action potential cannot be transmitted down the muscle cell by either direct or indirect stimulation clearly implicates the sarcolemma. The electronmicroscopic changes within the endoplasmic reticulum may give some indication as to the nontransmission of the action potential internally within the fiber, and if the endoplasmic reticulum is in continuity with the sarcolemma the increase in the total area involved would be such as to raise the resistance to that magnitude which would stop the propagation of the action potential. Further studies on enzymatic carbohydrate metabolism should be done in both of these disorders.

MITOCHONDRIAL ABNORMALITIES OF MUSCLE

Luft and colleagues presented in 1962[22] a new disorder of striated muscle in a 35-year-old patient whose symptoms dated back to the age of 7. In this patient there was profuse perspiration, polydipsia, thinness and progressing weakness. There was profound muscular wasting and weakness and an electromyogram was myopathic. There was a creatinuria. The main point of interest was a BMR between +150 and +200 per cent in the presence of a normal thyroid function. Both subtotal thyroidectomy and the administration of iodine and thiouracil had but minimal effects on the BMR. These investigators felt that their findings were not consistent with any previously known muscle disorder. An electronmicroscopic examination of the patient's skeletal muscle revealed a vast increase in the number of mitochondria in the perinuclear areas of the fibers. The mitochondria were of extreme variability in size, many of them being of giant size and containing a vast amount of densely packed cristae. Tubular types of endoplasmic reticulin were found within such mitochondria. Some had opaque bodies within them and others had dense, regularly layered cores. Still others were cylindrical and were surrounded by concentric sheaths. The biochemical studies of such muscle were restricted largely to a mitochondrial fractionation and revealed a loosely coupled state of oxidative phosphorylation. This was characterized by a nearly maximal rate of respiration in the absence of phosphate acceptor parallel to a normal phosphorylation when phosphate acceptor was present. Sensitivity of the respiration to oligomycin was only partial and the mitochondria exhibited a high magnesium-dependent ATPase activity which was only slightly stimulated by dinitrophenol. These investigators fractionated the muscle homogenate and revealed that there was a three- to fourfold increase in the total mitochondrial protein together with an increased cytochrome oxidase activity per unit of mitochondrial protein. Thus, they have come to the conclusion that this was a hypermetabolic state caused by an abnormal quantity and type of mitochondria in which there was an abnormal organization of the normal mitochondrial enzymes and that this resulted in a severely lowered capacity for respiratory control. This, then, is the first purely mitochondrial disorder of striated muscle.

ENDOCRINE MYOPATHIES

Since the cationic content of the muscle cell as well as the glycogen and protein metabolism are under endocrine control, it is not therefore surprising that many abnormalities of striated skeletal muscle are associated with dysfunctions of these particular glands. The cationic concentration of the muscle cell is largely under the control of the parathyroid gland, the adrenal gland and the pituitary. Dysfunctions of these cells will therefore result in aberrations of muscle contraction and muscle strength.

Perhaps more extensively than any other single gland, the thyroid has been studied in disorders of the muscle cell. As noted previously, the thyroid has as its peripheral receptor the mitochondria of the muscle cell. Brain[2] has classified the disorders of muscle associated with disorders of the thyroid gland as follows: (1) Disorders of muscle directly related to the thyroid gland. In this category he places chronic thyrotoxic myopathy, exophthalmic ophthalmoplegia and acute encephalomyopathy. (2) Disorders of muscle which have their ordinary clinical appearance radically changed by thyroidial disorders and in which the incidence of thyroidal disorders exceeds that of the normal population. In this category he places myasthenia gravis and familial periodic paralysis. Recent studies on the interaction of the thyroid gland in the latter two disorders have aided in clarifying the effect of the metabolic rate upon such disorders.

It has been noted for many years that hyperthyroidism may be accompanied by weakness of the proximal pelvic muscles and a marked excretion of creatine and that these changes may be reversed by iodine therapy. The usual picture is that of muscular weakness and fatigability and it is of interest that in many cases of thyrotoxicosis there may also be an increase in the size of the thymus gland. McEachern,[26] Thorn,[45] and others have studied this disorder in detail. The clinical disorder is characterized by a generalized muscle weakness more predominant, however, in the proximal muscles. Fifty per cent of cases so reported have demonstrated fasiculations and may hence resemble amyotrophic lateral sclerosis. The condition occurs predominantly in late middle age and may occur in people in whom the usual signs of hyperthyroidism, such as tachycardia and exophthalmos, may not be observed. Roche[33] and his colleagues have demonstrated with N^{15}-labelled glycine that creatine is formed normally in muscular dystrophy but that creatinine does not contain the label, showing that the creatine cannot be utilized by the muscle cell. Similar attempts have been made to do such studies in thyrotoxic myopathy but the picture to date has not been clear. There is, however, but little evidence that creatine itself has any marked derangement in thyrotoxic myopathy. Therefore, the site of the defect again would appear to be within the muscle cell, and in particular, the mitochondria. If such patients are fed glycine, an increase in the amount of creatine is also found. This represents a striking parallel to the creatine metabolism of muscular dystrophy. The only striking difference is that iodine or thiouracil will correct this metabolic abnormality in a hyperthyroidal patient. Askanazy[1] gave the first description of the pathology of the muscle in hyperthyroid myopathy, in which he noted extensive degenerative changes and described these as lipid infiltration, vacuolation, atrophic fibers and loss of cross-striations. More recent work has demonstrated that the majority of the changes described by Askanazy were artifactual except for the lipid infiltration. Nineteen cases of thyrotoxic myopathy have been examined in this laboratory and in none could architectural changes of muscle fibers be found.

The term "exophthalmic ophthalmoplegia" was also introduced by Brain,[2] in 1938, to describe a condition in which there is a malignant exophthalmos with swelling of the eyelids, edema of the conjunctiva and, in particular, paralysis of ocular muscles. Brain differentiated this condition from the hyperthyroid myasthenia gravis by the presence of ptosis in the latter disease and by the fact that the exophthalmic ophthalmoplegic patient did not respond to neostigmine. It is of interest that after correction of the thyrotoxicosis frequently this condition becomes worse. The question naturally raised is whether such a condition is secondary to thyrotoxicosis or to thyrotropic hormones. Although few studies have been done in recent years to clarify the disorder within the muscle, the studies of Marine and Rosen,[23] and more recently of Dobyns[5] have shown that the exophthalmos is not due to thyrotropic hormone but instead to a separate pituitary hormonal element which is released when excess thyroxin depresses TSH. These authors term this the "pop-eye" factor of the anterior pituitary. This observation could account for the fact that the TSH is elevated in only 50 per cent of the cases of exophthalmic ophthalmoplegia. Exophthalmic ophthalmoplegia may be differentiated from the exophthalmos associated with Graves' disease by the extreme ocular paresis. Early paralysis of external ocular muscle is a bad prognostic sign. Biopsy of such muscle demonstrates loss of cross-striation and flocculation of muscle fibers with phagocytosis. Naffziger[27] believed that these muscle changes were the sole reason for the poor prognosis; however, Rundle[34] and his associates have demonstrated that an increase of fat in the orbital content is responsible for the exophthalmia, although the muscle changes are no doubt the cause of the ophthalmoplegia. Thus, in summary, it is the consensus that exophthalmic ophthalmoplegia may be considered to be a disorder of a specific exophthalmic pituitary hormone and not just simple thyrotoxic myopathy. The treatment, therefore, leads to the paradox of giving small amounts of thyroid hormone in addition to a specific agent such as propyl thiouracil or iodine to combat the thyrotoxicosis. In 25 per cent of the cases even this treatment will not be of value. To preserve vision and prevent chemosis within the affected orbit, the Naffziger[28] operation was created in which deroofing of the orbit may be indicated to preserve vision. More recently a direct attack on the anterior pituitary has been attempted, and we have seen one case in which a dramatic reversal of this syndrome followed anterior pituitary surgery. It is of interest that with the exophthalmic goiter of Graves' disease there is a proportion of 9 females to 1 male, whereas with exophthalmic ophthalmoplegia not only is age of onset later in life but the strong sex differentiation appears not to be present.

Waldenstrom[46] created the term "acute thyrotoxic encephalomyopathy." He distinguishes this disease from chronic thyrotoxicosis by its impact upon bulbar muscles accompanied by fasiculations, tremors, delirium and coma. The syndrome is serious and will lead to death unless early treatment directed toward the thyrotoxicosis is started. It is of interest that in this one disorder, in addition to a creatinuria, there may be a creatininuria; this has been interpreted as secondary to an increased glomerular circulatory flow.

The finding of an athyroidal myasthenic patient by Drachman[6] has allowed the story of the effect of thyroid on myasthenia gravis to be completed. In the initial studies by Engel[8] it was clearly demonstrated that hypermetabolism and not TSH was responsible for increasing severity of symptoms in a patient with myasthenia gravis. By blocking the thyroid action, Engel was unable to demonstrate clearly the relation of hypometabolism to myasthenia gravis. Drachman, however, with an athyroidal patient was able to demonstrate a similar effect on myasthenia gravis by hypometabolism. It would appear therefore that a deviation in either direction from the euthyroid state tends to increase the severity of the symptoms of myasthenia gravis.

In a remarkably lucid study Engel[9] was able to demonstrate in familial periodic paralysis that the amount of paralysis was not dependent upon TSH or upon thyrotoxicosis but was in inverse proportion to the metabolic rate of muscle. He carried out this study by using small doses of T3 (triiodothyronine) and thus successfully blocked the pituitary gland, as measured by the radioactive iodine uptake, without creating thyrotoxicosis; his patient did not become worse. He then deliberately made the patient thyrotoxic with T3 and again no increase in symptomatology was noted. When, however, T3 was stopped and the metabolic rate fell, the patient became much worse. At this time TSH was released from the pituitary. To distinguish the falling metabolic rate from the release of TSH Engel then added exogenous TSH and again made the patient thyrotoxic, and the patient improved. This study has been verified by Norris[29] in both familial and sporadic paralysis.

The irritability of the muscle fibers may be expressed by the equation

$$\frac{Na^+ + K^+}{Ca^{++} + Mg^{++} + H^+} = I.$$

Endocrine abnormalities, in particular of the adrenal gland and parathyroid, may therefore affect this irritability constant. Hypokalemia may be associated with Cushing's disease or with a massive administration of adrenal steroids; whether it is the cause of or is coincident with the muscle changes in so-called cortisone myopathy is not known. Cushing, in his original description of the disorder bearing his name, included a moderate or severe weakness predominantly of the gluteal and iliopsoas muscles, and noted wasting of the glutei. Biopsies of muscles of patients with Cushing's disease have revealed in the past both neuropathic and myopathic lesions. It is also of interest that the basal metabolic rate in Cushing's disease is increased, indicating a mitochondrial abnormality, but the cause is not known. Primary adrenal tumors in which aldosterone is released may precipitate eposidic flaccid paralysis as part of this syndrome, in which there is potassium wastage and sodium retention. Crane and his associates[4] have noted a fourfold decrease in the biological decay time of Na^{22} after removal of an adrenal tumor from a patient with primary aldosteronism. In addition to their effect upon cations within the muscle cell, the steroids—in particular 11 and 17 oxysteroids—play an important part in the regulation of carbohydrate and protein metabolism. This has been noted particularly in the facilitation of the protein breakdown from amino acids to keto acids, which are then converted to glucose, and the nitrogen formed is excreted as ammonia or urea. Thus these steroids may have their effect upon the striated muscle cell and its cationic content or upon carbohydrate and protein metabolism as well as upon the mitochondria of the cell.

In Addison's disease, which is the converse of Cushing's disease, involvement of striated muscle is also suggested by the presence of flexion contractures. Thorn[44] believes such contractures to be the result of excessive accumulation of sodium in the collagenous connective tissue; the latter acts like extracellular sodium. Since the parathyroid, through its effect upon the kidney, has considerable control of calcium metabolism, it is not surprising that abnormalities of striated muscle are manifest in both hypo- and hyperparathyroid states. In hyopoparathyroidism there is a hypocalcemia and this has its primary manifestation through increased neuromuscular excitability, according to the formula shown above; thus, a decrease of calcium leads to increased irritability.

If there were a decrease of calcium and a decrease of potassium, these would tend to cancel out and tetany would not be manifest. If, however, potassium is then given to such a patient, tetany would reappear. In pseudohypoparathyroidism the parathyroid gland is normal or increased in size but the end organs are not receptive and the patient presents the symptoms of hypoparathyroidism. Such patients as these, however, present usually with a round moon face, and the index finger is usually the longest. These patients do not respond to parathormone but do respond to AT 10. The increased excitability of the muscle fibers is manifest by the typical carpal-pedal spasm and by Chovstek's sign; such patients may also have seizures, numbness and tingling of the extremities and lips, cataracts and enamel defects of the teeth. In the hyperparathyroid state the common picture is that of fatigue, weakness and aching in the muscles, and a fluctuating decrease of the deep tendon reflexes. If this condition is severe there may be accompanying anorexia, nausea, vomiting and constipation. Since one of the main functions of the parathyroid gland is that of tubular reabsorption of phosphate, there may be an increased rise in calcium as the phosphate falls. This then would lead to an increased calcium in the urine and metastatic deposits of calcium as well as bone lesions due to withdrawal of the calcium of bone. Recent studies by Neuman[14] have shown that one of the primary effects of parathormone is on bone citrate with a secondary increase of calcium other than through the renal tubule.

Finally one is left with the abnormalities of striated muscle associated with pituitary gland abnormalities. Wasting of muscles, in particular of the distal muscles of the upper extremity, has long been noted as an accompanying manifestation of acromegaly. What is not certain is whether such wasting is due to endomysial changes within the muscle or to endoneural changes in the nerve accompanying this disorder as well as carpal tunnel entrapment of the peripheral nerves on their way to the hand. Approximately 50 per cent or more of acromegalic patients complain of muscle weakness and fatigue, and this may be confirmed by testing of the motor power in the ordinary clinical examination.

EMBRYOLOGIC ABERRATIONS: GENERALIZED MYOSITIS OSSIFICANS

This rare disorder is presumed to be of embryologic derivation. In favor of this presumption is the association of congenital malformations, predominantly of skeletal nature, affecting usually the great toe or the thumb, in almost 75 per cent of those afflicted. The appearance is that of a microdactylia due to ankylosis or synostosis of the interphalangeal joints and the absence of one phalanx of the digit involved. The absence of incisors and ear lobes may occur but not as commonly.

Either spontaneously or secondary to trauma, large areas of bone may be laid down in skeletal muscle, giving rise to bizarre deformities and limitation of movement of the extremities. A family history is not uncommon.

The onset is heralded by swellings of various consistencies anywhere over muscle tissue. Usually this swelling is initially soft and/or fluctuant but it may be bone-hard. Nuchal and paraspinal muscles, the adductors of the lower extremities, and those muscles attached to the scapulae are more commonly involved. The tongue, larynx, diaphragm and eye muscles have the least involvement.

Biopsy of involved areas has shown initially collagen and reticulin with little hemorrhage or inflammation. Later, cartilage and spicules of bone are found. The transition between involved and normal muscle is usually abrupt and dramatic. Occasional intact muscle fibers are seen within bone and muscle. "Buds" are common at the margin.

The disorder appears to be an altered embryonic differentiation of mesenchymal tissue in which muscle cell is replaced by connective tissue, which in turn condenses to form osteoid tissue much as in the formation of the fetal skeleton. The alkaline phosphatase of the heterotopic bone is said to be higher than that of normal bone.

AMYLOID DISEASE

Primary amyloidosis has long been associated with muscle weakness. Amyloid appears to be an abnormal protein complex with a sulfate-bearing polysaccharide. It is a substance not unlike heparin, but it is not susceptible to hyaluronidase. It is only in the primary form of this disease, and in particular in the familial cases recorded, that muscle and nerve are predominantly involved. Amyloid found in the primary disorder stains differently from that deposited in secondary amyloidosis or multiple myeloma. The onset of the disorder is usually at about the age of 50. The amyloid substance is laid down in the blood vessels, connective tissues and the endomysium of striated muscle. The skin, heart, gastrointestinal tract and tongue may also be involved. Unlike secondary amyloidosis, however, the liver and kidney are but minimally involved. The usual clinical picture is that of cardiac enlargement, macroglossia and focal deposits in the tracheal larynx and gums.

Proximal muscular wasting and weakness and involvement of major peripheral nerves have been noted. More recently it has been noted that there are almost pathognomonic infiltrations in the vitreous of the eye. These opacities consist of cellular as well as membranous or veil-like deposits and have a waxy contour resembling that of glass wool. The diagnosis may be confirmed by muscle biopsy, by biopsy of the gum or skin or by paracentesis of the vitreous. Biopsy demonstrates amyloid deposition to be within the endoperimysium and not within the muscle fiber itself. It is also found heavily about blood vessels, particularly the media of the involved blood vessels. Occasionally foreign body giant cells may be found around such deposits. Should such a disorder be suspected, slit-lamp examination of the eye may be extremely rewarding.

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Electroencephalography in Epilepsy

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ELECTROENCEPHALOGRAPHY must be approached in the light of current concepts of epilepsy. Almost a century ago, Hughlings Jackson wrote, "A convulsion is but a symptom." Today neurologists have elaborated this to the view that epilepsy is not a disease but a symptom-complex resulting from multiple causes which include such diverse processes as natal asphyxia, hereditary disorders of brain metabolism, traumatic scars and brain tumors. In evaluating patients with seizures neurologists seek to answer two questions: Where is the locus of abnormally irritable neurones and what is the underlying pathologic process producing this state of exalted irritability? To this end electroencephalography constitutes probably the most valuable laboratory examination employed in the study of patients with seizures.

In this paper, we hope to clarify the values and limitations of electroencephalography. We do not expect the reader to emerge prepared to interpret a recording, but, rather, we hope that he will come to a better understanding of the reports made by the electroencephalographer. At the outset, the reader must understand clearly that no electroencephalographic changes are pathognomonic of epilepsy. In other words, electroencephalography will not establish the diagnosis of epilepsy, save in the relatively uncommon circumstance of a clinical seizure occurring during the examination. *The diagnosis of epilepsy remains a clinical, not an electroencephalographic, process.* If it is recalled that epilepsy is but a symptom, a moment's reflection indicates the reasonableness of this view. The many acute and chronic diseases of the brain resulting in seizures have few common features; thus, the diversity of causes is reflected in an equal diversity of abnormal electrical signs.

Since electroencephalographers recognize no electrical sign peculiar to seizures, they must interpret the electroencephalogram in the light of the clinical problem. Ideally, an electroencephalographic report should consist of an objective description of the recording: the rhythms seen, their frequency, spatial distribution over the scalp, and response to changing physiologic states such as sleep, mental activity, and hyperventilation. Bearing these data in mind and armed with knowledge of the clinical problem, the electroencephalographer attempts to integrate all into a meaningful interpretation which may give valuable clues as to the site of origin of the epileptic process and in some instances also offer evidence as to the nature of the underlying pathologic process.

TECHNIQUE OF EXAMINATION

By processes not yet clearly understood, the brain generates potentials of approximately 15 to 100 microvolts, as they are detected on the surface of the intact scalp. These potentials consist of rhythmic sinusoidal oscillations ranging in frequency from about 1 to 40 cycles per second. In most subjects several frequencies exist, appearing as stable fields distributed over the scalp in a relatively stereotyped manner.

In many ways the electroencephalogram is analagous to the electrocardiogram, and the techniques for detection of the potential changes are similar. As with the electrocardiogram, potentials are detected by applying electrodes to the skin and connecting them directly to multichannel, ink-writing amplifiers. The technician affixes electrodes to the scalp in such a manner as to assure low interelectrode resistance. The type of electrode and manner of fixation vary in different laboratories. Similarly, no universal agreement exists as to the precise location and number of electrodes needed. Many laboratories use the so-called "10-20" system established by the International Federation of Societies for Electroencephalography. This system provides for precise measurement of the head and uniform placement of electrodes. The exact manner in which pairs of electrodes are coupled into the ink-writing amplifiers also varies in different laboratories. Relatively closely spaced electrodes, separated by approximately 3 cm., are termed "bipolar" derivations or montages. In the past, "monopolar" derivation referred to widely separated scalp electrodes and an electrode attached to the ear lobe, which constituted the common electrode in each channel of recording. The term "monopolar" proved misleading since it implied that the ear was a region of electrical silence. Experience has shown that electrodes affixed to the ear detect potentials from the inferior surface of the temporal lobe. More recently electroencephalographers have sought an indifferent electrode by using high resistances to connect all scalp electrodes into a common "reference" electrode. In general, the precise manner of electrode coupling depends upon the approach of the individual electroencephalographer. Today most electroencephalographers acknowledge the need for multiple derivations as well as different types of derivations. The examination necessarily demands flexibility in meeting different clinical problems. The procedure itself entails no discomfort to the patient and poses no problems even with infants and children.

Recurrently the question arises whether drugs should be discontinued prior to examination. In some instances, drugs undoubtedly exert a suppressive action, converting an abnormal record into a normal one. Nevertheless, since the demonstration of abnormal electrical potentials does not establish the *diagnosis* of a seizure disorder, we must weigh the danger that abrupt withdrawal of drugs may precipitate seizures or status epilepticus against the value of demonstrating abnormal potentials. Personally, we do not believe the information gained compensates for the risk. Consequently, we do not routinely discontinue anticonvulsant drugs prior to examination. Exceptional circumstances may justify stopping drugs. Such withdrawal should be carried out under the supervision of someone familiar with both clinical and electroencephalographic problems.

In many instances the appearance of abnormal electrical activity depends upon the physiologic state of the patient. Thus, "epileptiform" activity may appear while the patient is awake, only to disappear when he sleeps. Conversely, a normal waking record may be disrupted by abnormal discharges as the patient drifts into drowsiness and sleep. Occasionally no abnormal discharges will occur during a recording lasting up to two hours. Failure to detect abnormality in patients who unquestionably have seizures often puzzles physicians. In the intervals between seizures, electrical abnormality appears intermittently and briefly; hence, the electrical sampling which constitutes the examination may be taken during a period of relative electrical normality. If it is recalled that two hours constitute less than 10 per cent of a day, the observation seems less puzzling. By analogy, fires occur in a large city every day, yet one may drive about the city for many days without seeing a fire truck.

Because of the evanescent nature of the abnormality, the electroencephalographer seeks to assure the occurrence of all physiologic states which may permit abnormal discharges. Whenever possible, we prefer to begin the examination in the so-called "basal state" with the patient sitting or lying quietly keeping his eyes closed. After an appropriate time, should no abnormality appear, the patient can be allowed to drift into drowsiness and sleep. If the waking record is normal or discloses only "nonspecific" abnormality, which will be described subsequently, we believe that making recordings from the patient during the sleeping state becomes mandatory. We shall discuss procedures such as hyperventilation and photic stimulation, executed to "activate" abnormality, in a subsequent section.

THE NORMAL ELECTROENCEPHALOGRAM

As we mentioned previously, the electroencephalogram consists of rhythmic sinusoidal waves distributed in a stereotyped fashion over the scalp surface. Hans Berger, the "father" of electroencephalography, introduced the custom of denoting the frequency of the waves by different Greek letters. By convention, the term "alpha" rhythms refers to frequencies of 8 to 12 cycles per second; "beta" rhythms, to frequencies between 20 and 30 cycles per second; "theta" rhythms, to frequencies between 4 and 7 cycles per second; and "delta" rhythms, to those less than 4 cycles per second.

First we shall discuss the adult electroencephalogram since its relative simplicity makes it more readily comprehensible to the reader. When the patient rests quietly with his eyes closed, in a so-called basal or "resting" state, alpha rhythms occur over the occipital region (Fig. 1). They may consist of unceasing oscillations but more commonly appear in recurrent bursts. They arise from relatively discrete fields symmetrically disposed over homologous areas of the occipital region. The waves from the homologous regions appear virtually simultaneously (bisynchronously). When most persons open their eyes, alpha rhythms disappear (blocking). Mental activity, such as solving a simple sum, also "blocks" alpha rhythms.

Beta rhythms occur less commonly and usually are most conspicuous in the region of the sensori-motor cortex. Superficially resembling, but nevertheless clearly distinct from, alpha rhythms are so-called "mu" or "wicket" rhythms. These, too, arise from the sensori-motor region and are inhibited by motor acts such as clenching the fist.

As a rule, theta rhythms are absent during the basal state. Nevertheless, in some normal adults without known neurologic disorder, theta rhythms do occur in the "resting" record, being most conspicuous in the temporal regions. Occurring in perhaps 5 to 10 per cent of a presumably healthy population, they have no known significance. Perhaps the reader may best envision them as "normally abnormal" records. Delta activity never occurs normally in the waking record of adults.

With the onset of drowsiness the basal recording changes strikingly. Alpha rhythms cease and low-voltage theta activity appears diffusely over the head. As the patient drifts from drowsiness into light sleep, transient discharges termed vertex or "V" waves erupt bisynchronously in the parietal regions near the vertex (Fig. 1). Brief bursts of bisynchronous, symmetrical, 14 cycle per second rhythms called "sleep spindles" soon appear. As the patient falls more deeply asleep, high-voltage, irregular delta activity becomes dominant.

From the natal period to the age of 20 to 25 years complex maturational changes characterize the electroencephalogram, after which the

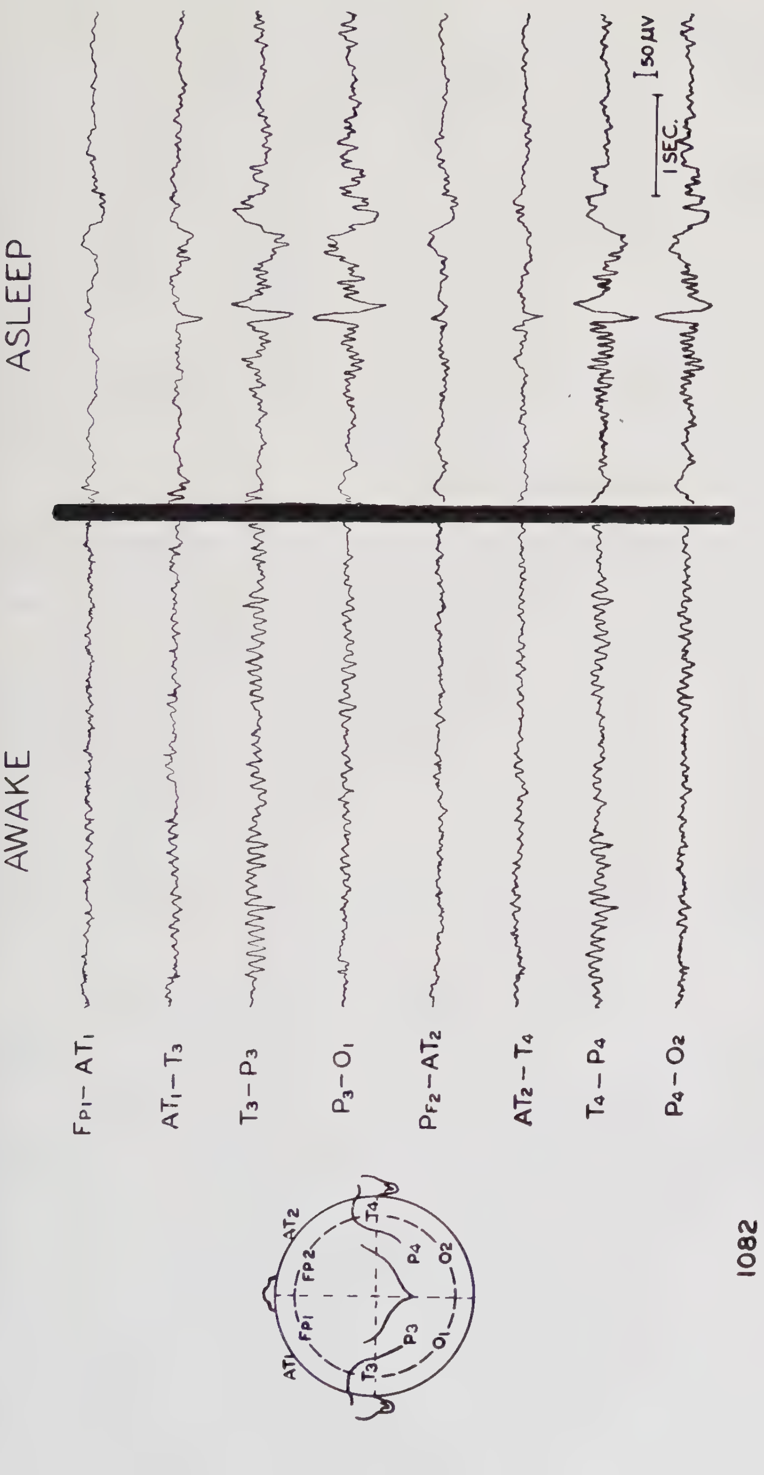
AWAKE
ASLEEP
FP1 – AT1
AT1 – T3
T3 – P3
P3 – O1
PF2 – AT2
AT2 – T4
T4 – P4
P4 – O2
50 µV
1 SEC.
AT1
FP1
FP2
AT2
T3
P3
O1
O2
P4
T4
1082

Fig. 1. Normal electroencephalogram in adult. In waking record (left panel) note alpha rhythm in channels 3 and 7. During sleep (right panel) note 14 per second spindles and "V" waves (channels 3, 4, 7, and 8).

rhythms just described typify the record. Little rhythmical activity occurs in the electroencephalogram of a neonate, but within a few weeks bursts of sinusoidal rhythms appear. Initially these bursts are not well formed nor do they occur bisynchronously. Until the age of five or six years, theta frequencies characterize the record. After this, rhythms in the alpha range evolve. Subsequently, the electroencephalogram matures gradually toward the adult form, theta rhythms being less conspicuous and alpha rhythms becoming more persistent and better organized. During adolescence, irregular slow discharges of low to moderate voltage may interrupt the smooth oscillations of the alpha activity.

When the child sleeps, the record assumes the same general character as in the adult, with slow frequencies, spindle rhythms and vertex waves. However, in sleep, too, the electroencephalogram of the child is distinct from that of the adult, several features distinguishing it from the mature record.

Finally, as the senium approaches, further changes occur. These begin at about 60 years of age in subjects who have no demonstrable neurologic deficits or diseases.[13] They consist of irregular slow discharges of delta frequency, usually seen in the temporal regions and, curiously, more often on the left side. Diffuse theta rhythms can also appear. Obrist, Busse and Henry[10] have offered evidence suggesting an inverse correlation in the incidence of these changes with the level of systolic blood pressure. While the significance of these findings remains unclarified, they compound the electroencephalographers' problems of interpretation since they do not necessarily signify clinically demonstrable abnormality.

This brief survey has demonstrated the complexity and maturational variabilities of the electroencephalogram. It also indicates clearly the necessity for an electroencephalographer to have thorough familiarity with the normal electroencephalogram and its variations.

THE ABNORMAL ELECTROENCEPHALOGRAM

Electroencephalograms of patients who have seizures exhibit many different abnormalities. At the present time electroencephalographers cannot agree on a general classification of these abnormalities. As we have mentioned, no change in the electroencephalogram is pathognomonic of seizures, so that the term "epileptic discharge" lacks precise meaning. Certain types of abnormality occur with greatest frequency in patients who experience seizures; for this reason we refer to them as "epileptiform" abnormalities. Other abnormalities appear in many neurologic diseases not regularly accompanied by seizures; these we term "nonspecific" abnormalities. Lastly, certain patients who experience seizures have normal electroencephalograms in the interictal period. Each of these categories we shall discuss separately.

Epileptiform Discharge

The electrical abnormality most consistently associated with seizures is a sporadic, transient wave having a duration of less than 80 milliseconds. Electroencephalographers refer to such a discharge as a "spike." In addition to the form or "morphology" of the spike, the electroencephalographer considers its location, which may be classified as focal, multiple or bisynchronous.

FOCAL SPIKE DISCHARGE. A spike is described as "focal" if it appears consistently from a circumscribed area of the scalp. Usually spikes appear as a random discharge, repeated at irregular intervals (Fig. 2). Less commonly, spikes may repeat rapidly in a rhythmic or semirhythmic fashion. They may occur during the waking record and remain during drowsiness and sleep or, occasionally, may disappear during sleep. In some instances, spikes appear infrequently or not at all during the waking record, but make their appearance with the onset of drowsiness and persist during the deepening phases of sleep. Spikes recorded from the temporal region often exhibit this pattern.

In adults, focal spike discharges tend to be unchanging and usually are associated with an atrophic epileptogenic lesion, such as a post-traumatic meningocerebral cicatrix, residuum of encephalitis or meningitis, or ischemic cortex from whatever cause. The form of the spike does not vary in different cortical areas and of itself offers no hint as to the clinical pattern of the attack. On the other hand, the cortical localization of the spike focus can correlate with the clinical type of seizure; for example, a spike focus found in the temporal lobe is often associated with seizures characterized by psychic auras, autonomic events and automatic behavior—so-called temporal lobe or "psychomotor" seizures. Conversely, a spike focus localized in the rolandic region is more likely to be associated with focal somatomotor (Jacksonian) seizures. Occasionally, despite a clear-cut focus, the patient has only generalized convulsions.

In some instances spikes may have a duration greater than 80 milliseconds. Electroencephalographers refer to these prolonged or "slow" spikes as "sharp waves." Such discharges, having a duration of 80 to 200 milliseconds, probably signify that the recording electrodes lie at a distance from the source of the epileptiform discharge. The prolongation of the spike presumably results from temporal dispersion of the initial discharge by conduction in cortical fiber systems.

MULTIPLE FOCI. The electroencephalograms of some patients may show evidence of multiple sources of spike discharges. When discharges arise independently from several unrelated areas, electroencephalographers assume the existence of independent discrete foci of abnormal cortical activity. Diseases productive of generalized disturbances in cerebral function—for example, meningitis, encephalitis, metabolic or degenerative brain diseases—are most commonly incriminated. The electroencephalograms of such patients, although implying extensive cerebral changes, usually cannot suggest specific underlying causes.

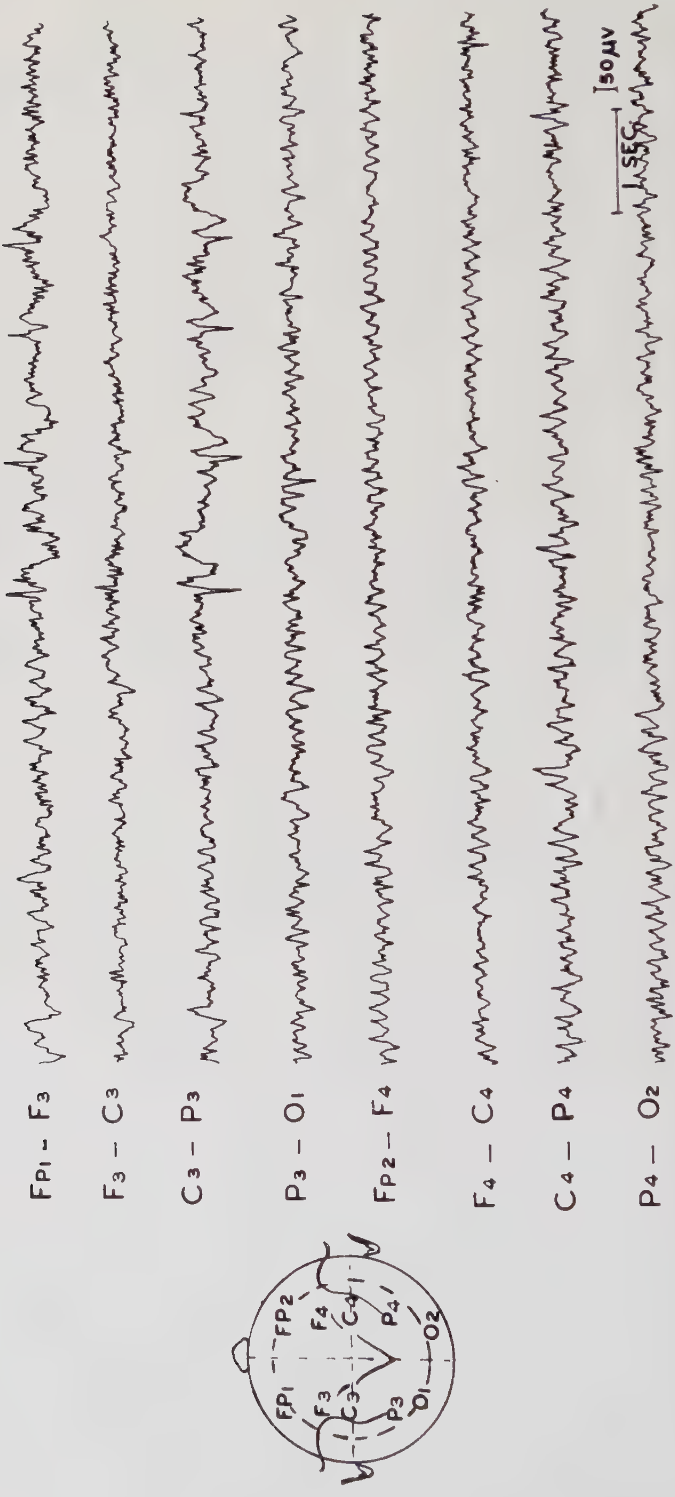
FP1 – F3
F3 – C3
C3 – P3
P3 – O1
FP2 – F4
F4 – C4
C4 – P4
P4 – O2
50 μV
1 SEC
FP1
FP2
F3
F4
C3
C4
P3
P4
O1
O2

Fig. 2. Focus of spikes, having traumatic origin, in left rolandic area of 22-year-old man. Seven years previously patient sustained subdural hematoma with residual right hemiplegia and aphasia. Seizures consist of twitching in right hand spreading to arm and face and occur infrequently. Note spikes in channels 1 and 3, indicating origin in area embraced by F_3 and C_3.

Gibbs and Gibbs[4] introduced the term "hypsarrhythmia" in reference to electroencephalograms showing diffuse high-voltage slow waves interspersed with spike discharges which may be multiple and asynchronous or diffuse and synchronous. Although seen primarily in infants and young children, these changes in the electroencephalogram are not characteristic of any single convulsive disorder.[6] Children with phenylketonuria, pyridoxine deficiency, cerebral lipoidosis or the residuals of severe birth asphyxia may all have indistinguishable electroencephalograms. In a rather large percentage of children having hypsarrhythmic changes in the electroencephalogram, the cause of the illness is unknown. Rather than looking upon this as a clinical entity, many electroencephalographers view these changes as the consequence of a severe widespread insult to the maturing brain. This hypothesis finds support in the observation that, as these children grow older, the abnormalities may evolve into focal discharges or, occasionally, may disappear entirely (Fig. 3). Despite this apparent amelioration of the abnormality, these children face a grim future, many suffering severe mental retardation.

Infrequently, two foci may exhibit complex interrelationships, particularly when they appear in homologous areas of the cerebral hemispheres. In such instances, one may observe discharges consistently initiated in one hemisphere and followed, after an interval of some milliseconds, by a comparable discharge in the homologous area of the opposite hemisphere. This process, termed "cross-firing," presumably results from transmission of the discharge through commissural fiber systems to the opposite hemisphere. In other instances, although the majority of discharges arise in one hemisphere, occasional independent discharges appear in the opposite hemisphere. Electroencephalographers refer to the area of predominant discharge as the "primary" focus and to the area in the other hemisphere as a "secondary" or "mirror" focus. At times, differentiation between mirror foci and independent foci is difficult. In a mirror focus the cortex presumably is not intrinsically epileptogenic but has become so by the constant bombardment from the primary focus. In some instances removal of the primary focus by surgical means results in the disappearance of abnormal discharges from the mirror focus.

Although spike discharges may appear during the interictal period, surprisingly, a simple increase in the rate of firing of the spikes usually does not characterize a seizure. Instead, during the clinical attack spike discharges often cease, being replaced by sustained sinusoidal rhythms. The rhythmic activity may evolve in the local area from which spikes arose or may appear from all head regions. The physiologic significance of this transition from episodic to persistent discharge remains enigmatic.

BISYNCHRONOUS SPIKE-WAVE DISCHARGES. Bisynchronous spike-wave discharges were among the earliest abnormalities which electroencephalographers associated with seizures (Fig. 4). Commonly, spikes

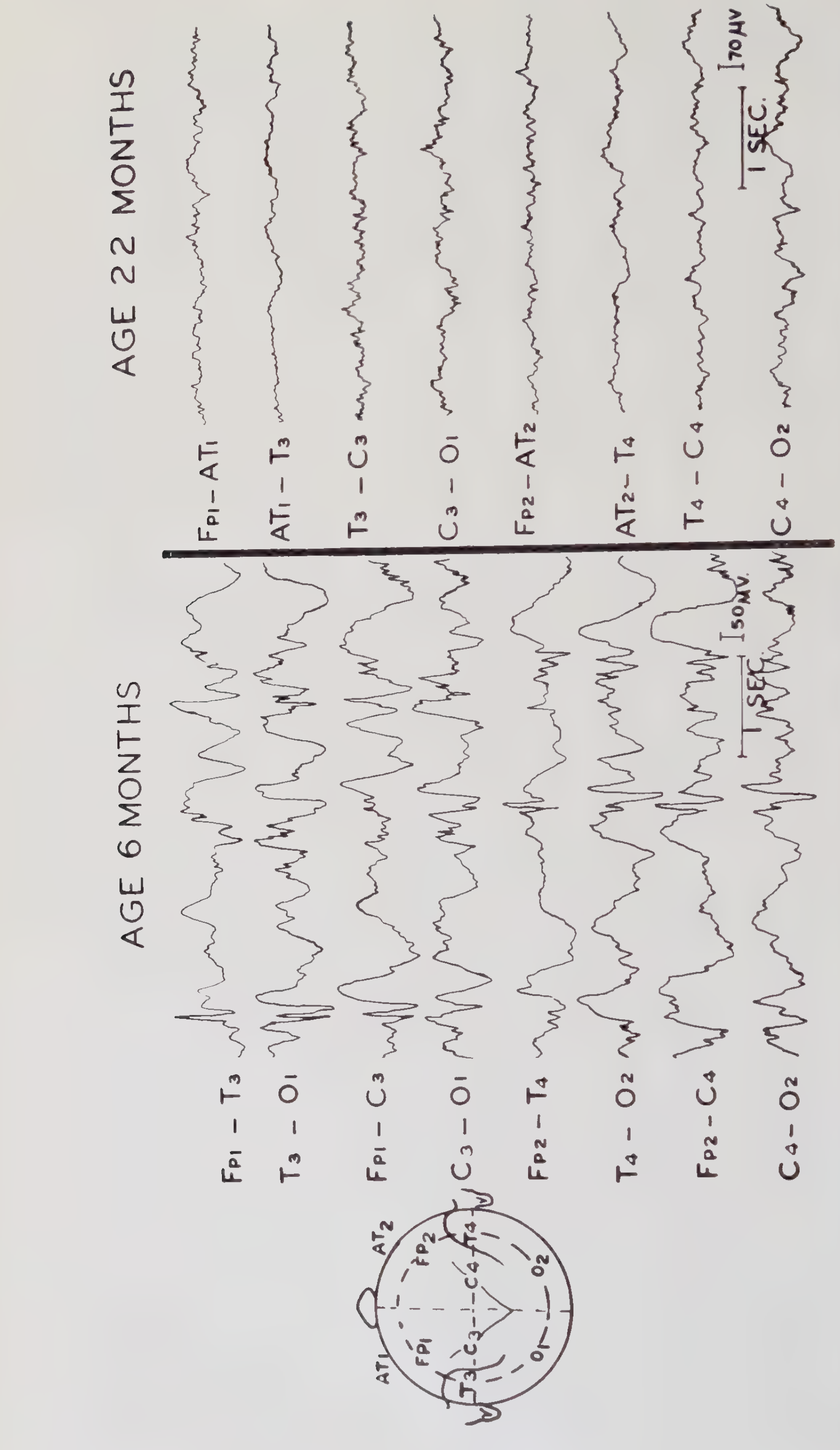
AGE 6 MONTHS
AGE 22 MONTHS
FP1 – T3
T3 – O1
FP1 – C3
C3 – O1
FP2 – T4
T4 – O2
FP2 – C4
C4 – O2
FP1 – AT1
AT1 – T3
T3 – C3
C3 – O1
FP2 – AT2
AT2 – T4
T4 – C4
C4 – O2
1 SEC.
50 µV.
70 µV
AT1
AT2
FP1
FP2
T3
C3
C4
T4
O1
O2

Fig. 3. Evolution of "hypsarrhythmic" record in microcephalic child with mental retardation and frequent minor seizures. At time of second recording seizures had virtually ceased although severe retardation persisted.

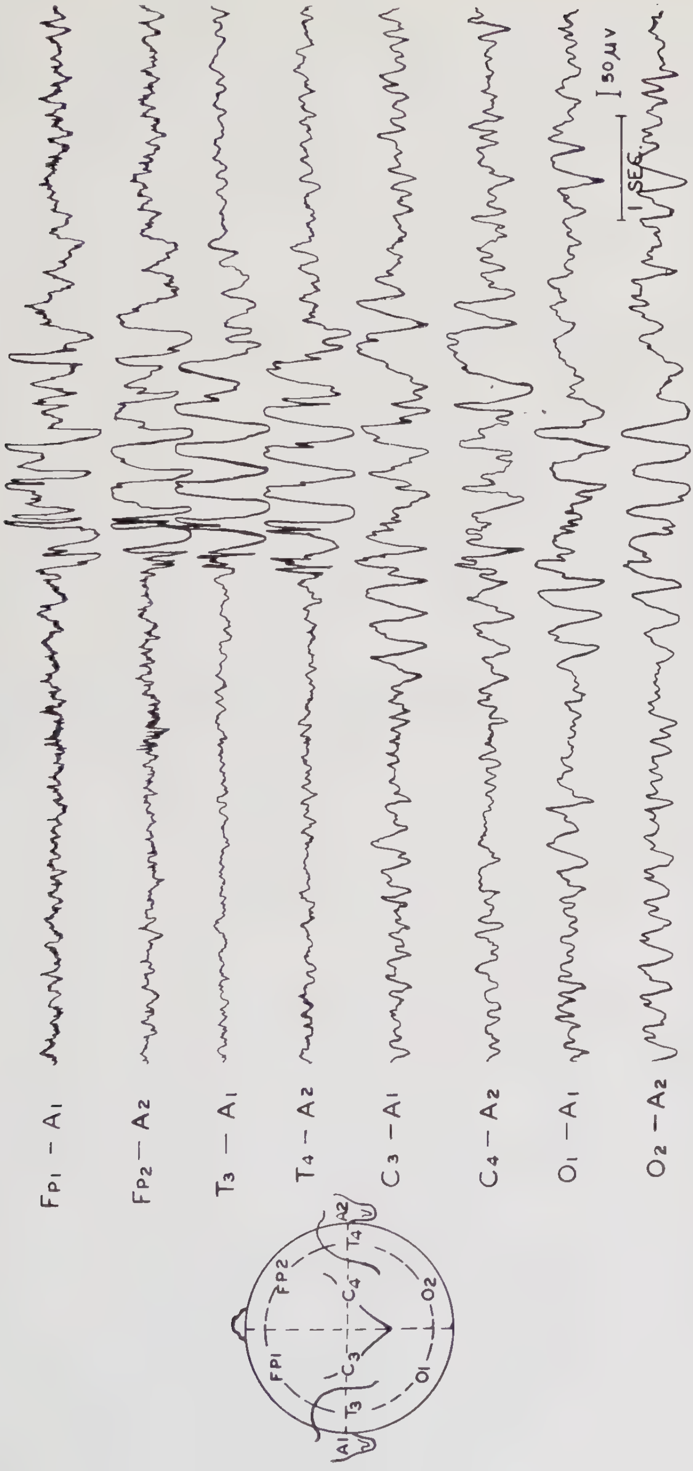
Fp1 - A1
Fp2 - A2
T3 - A1
T4 - A2
C3 - A1
C4 - A2
O1 - A1
O2 - A2
50 μV
1 SEC.
FP1
FP2
C3
C4
T3
T4
O1
O2
A1
A2

Fig. 4. Spike-wave bursts in 8-year-old boy with numerous petit mal seizures for 1 year. An older sister also has seizures.

appear virtually simultaneously in both hemispheres and are followed by slow waves of relatively great duration. The entire complex, repeating three times per second, constitutes the "classical" spike-wave discharge. The abnormality erupts abruptly from a background of normal electrical activity. Although the spike component of the complex has its greatest amplitude over the anterior head regions, the discharges appear diffusely over the skull. The paroxysms rarely last more than 10 or 15 seconds, disappearing as suddenly as they began. During sleep the bursts usually become shorter in duration; at times only a single spike-wave complex appears. If repetitive bursts occur in sleep, they often are less stereotyped than in the waking record. In patients with petit mal seizures, hyperventilation regularly produces attacks which are accompanied by bursts of spike-wave discharge.

Originally electroencephalographers believed that 3 per second spike-wave discharges consistently accompanied "petit mal" seizures, short interruptions of consciousness lacking premonitory symptoms and having minimal motor accompaniments. Recently the relationship has seemed less clear. Many patients suffering typical brief arrest of consciousness have electroencephalograms which differ from the typical 3 per second spike-wave pattern. Such divergences may be in terms of frequency of repetition, spatial distribution of the spikes or unilateral initiation.[9] Conversely, careful observation of patients during bursts of typical spike-wave discharge discloses many behavioral alterations other than simple arrest of consciousness. Some patients smack and lick their lips, movements previously thought typical of seizures arising in the temporal lobe. Other patients may yawn, smile, cough, mutter or make other complex purposeful acts. In any given patient one may observe a spectrum of seizures ranging from simple arrest to complex motor acts which at times seem determined by fortuitous environmental circumstances.

Nevertheless, despite the variability in electrical events and ictal behavior, there remains a "core concept" of petit mal epilepsy which has meaningful clinical connotation. Typically, the disease begins in a child of five or six years of age who has previously been without neurologic disorder. During infancy and early childhood the electroencephalogram is normal, spike-wave activity emerging at about the same age as clinical seizures appear. Metrakos and Metrakos[7] have shown that this type of convulsive disorder has a strong genetic background, with a high incidence of seizures in the immediate family of the proband. Further, siblings without seizures may nevertheless show bursts of spike-wave discharges in their electroencephalograms (Fig. 5), implicating them as carriers of the disease. The appearance of the seizures at a relatively uniform age, the absence of demonstrable structural changes in the brain, and, usually, the spontaneous cessation of seizures during the third decade point to the possibility of an inherited defect in some

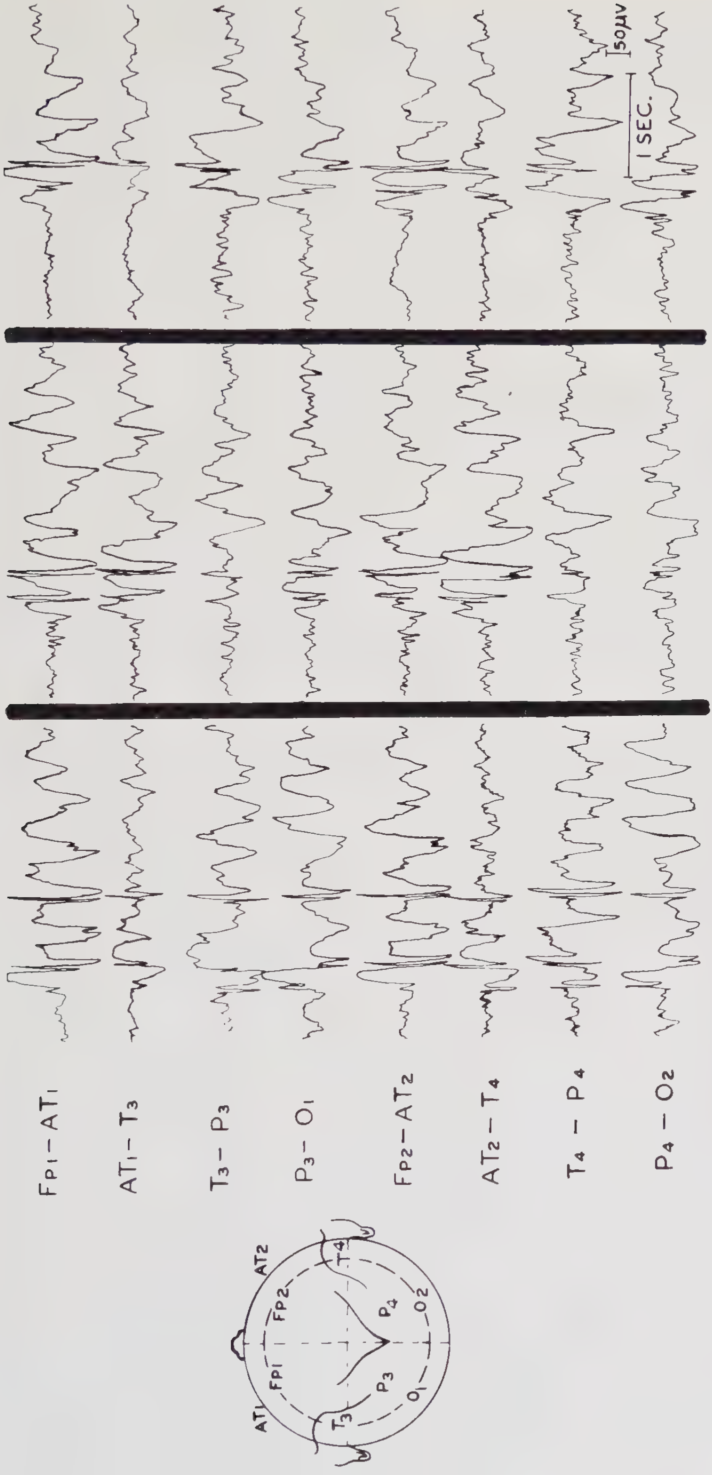
FP1 – AT1
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Fig. 5. Spike-wave bursts in asymptomatic 13-year-old sibling. Compare with Figure 4.

enzymatic system of the maturing brain. Such a hypothesis would explain the failure of true petit mal to develop after the age of 25 years.

Although the pathophysiology of petit mal epilepsy remains unclarified, experimental evidence from animals has suggested that the discharges may arise in such subcortical structures as the thalamus or brain stem.[5] In recent years the complexity of the problem has been increased by observations that a deeply situated focus in one hemisphere can initiate bisynchronous discharges bearing a strong resemblance to the spike-wave discharges of subcortical origin.[11] In such instances constant unilateral initiation of the spike-wave discharges or occasional unilateral bursts may constitute clues to the underlying focal abnormality. Differences in the rate of repetition of the spike-wave bursts, particularly in the direction of slow rates of repetition, may also suggest cortical initiation. Rovit, Gloor and Rasmussen[12] believe that intracarotid injection of amobarbital aids in the differentiation of cortical from subcortical epilepsy.

Nonspecific Abnormality

As a rule, nonspecific abnormalities consist of frequencies slower than those normally seen. Such abnormalities may be localized or diffuse.

FOCAL ABNORMALITY. Regardless of their nature, focal abnormalities arouse suspicion of an underlying structural lesion. Irregular slow discharges having an equivalent frequency of less than four per second (delta activity) usually signify relatively acute disturbances of cerebral function (Fig. 6). Silvermann and Groff[15] have shown that persistence of such discharges during sleep suggests a superficially located lesion On the contrary, disappearance is more likely to be observed in the presence of a deeply situated lesion. The abnormality itself gives no clue to the nature of the underlying process. Diseases as diverse as brain tumors, cerebral infarction, hemorrhage, brain abscess or focal encephalitis may produce indistinguishable electroencephalographic abnormalities. In some instances serial examination may provide a clue to the nature of the process.[3, 14]

Focal abnormalities recorded soon after a clinical seizure require special consideration. In some patients focal discharges may persist for several days after a seizure. Although it usually provides a reliable indication of the site of origin, such abnormality does not necessarily signify an underlying progressive structural lesion. In order to evaluate the significance of such abnormality, the electroencephalographer may request repetition of an examination after the patient has been without seizures for 10 to 14 days.

Focal abnormalities in the theta range (4 to 7 cycles per second) have even less certain significance. In many patients no demonstrable structural changes exist. In such a situation evaluation depends upon the clinical character of the seizure disorder. We would remind the reader

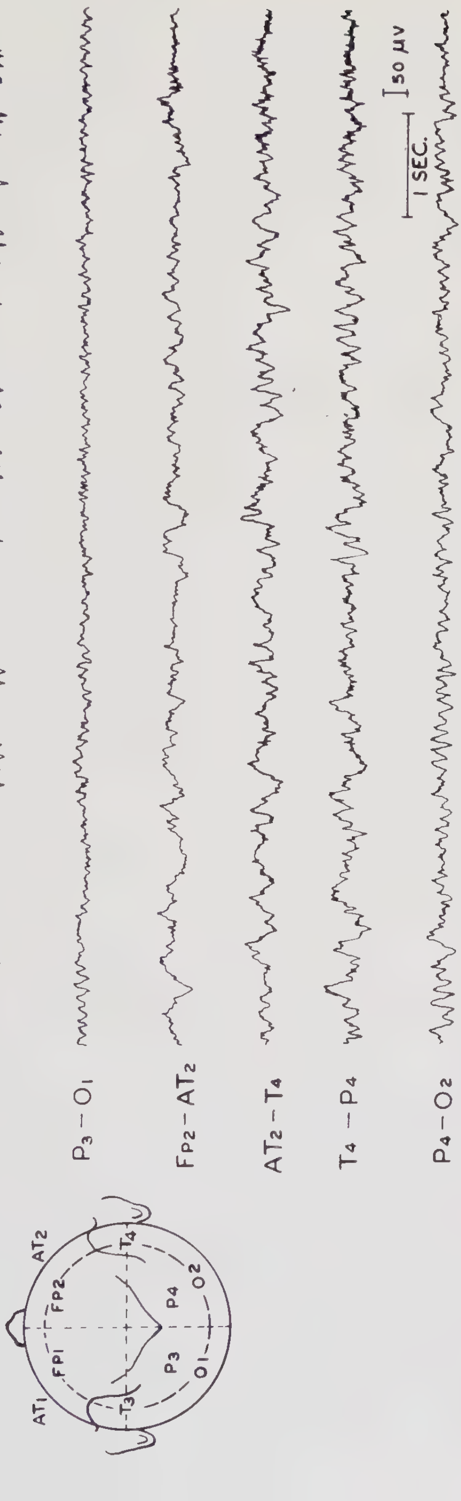
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Fig. 6. Focus of arrhythmic delta activity in 44-year-old man with astrocytoma of right temporal lobe and insula. Seizures consisted of foul taste followed by confused, automatic behavior. Note irregular slow discharges in channels 5, 6, and 7.

that the mere observation of theta activity in the electroencephalogram does not necessarily demonstrate any causal relationship since normal persons may have such frequencies in their electroencephalograms.

Diffuse Abnormality. Whereas the finding of focal abnormality in the electroencephalogram increases the suspicion of an underlying structural lesion in the brain, the same does not apply to diffuse abnormalities.

The appearance of rhythmic delta activity in the waking record of adults is unequivocally abnormal, signifying in most instances a severe but nonspecific disturbance in cerebral function. Trauma to the head, diffuse infectious processes, deep-seated tumors in the vicinity of the thalamus or increased intracranial pressure secondary to tumors in the third ventricle or posterior fossa may incite such abnormal rhythms. In most instances, seizures do not accompany these disorders.

In younger patients, rhythmic delta activity occasionally predominates over the posterior head regions. This abnormality must be distinguished from the irregular, nonrhythmic slow activity observed in the occipital regions of adolescent children. Children exhibiting rhythmic occipital delta activity commonly have seizures. Such delta rhythms appear in the interictal period, but generalized spike-wave discharges usually develop during the seizure itself.

The electroencephalographer always has difficulty in interpreting the significance of diffuse theta activity. Theta rhythms normally appear in the electroencephalograms of children and may persist into adolescence. Furthermore, approximately 5 to 10 per cent of apparently normal adults have theta rhythms in their basal recordings, the figure rising, as we previously mentioned, to an even higher percentage in a population of normal elderly people. Thus, the simple observation of theta activity in the record of a patient known to have seizures does not establish an unequivocally causal relationship between the two circumstances. On the other hand, many patients suffering seizures characterized by automatic activity show intermittent theta rhythms in their electroencephalograms during interictal periods and constant theta activity during an attack.

In recent years, electroencephalographers have devoted considerable attention[16] to the significance of discharges termed, by Gibbs and Gibbs,[4] "14 and 6 per second positive spikes." Occurring almost invariably during sleep, the discharges appear over the posterior temporal and occipital areas in large dipoles most readily detected by widely spaced "monopolar" derivations. In contrast to sleep spindles, 14 per second positive transients appear asynchronously in each hemisphere. Initially, the Gibbses related these discharges to clinical symptoms presumed to be epileptic. Other authors have claimed association with paroxysmal autonomic disturbances such as abdominal pain, nausea, vomiting and headache, or with psychiatric disturbances manifested by "aggressive behavior" and "disorders in adjustment." Early studies had suggested that such discharges tend to occur primarily in children and adolescents. Later observations have revealed a remarkably high incidence (30 per cent) in normal, healthy adolescents. We do not believe these discharges possess clear and consistent association with any clinical disorder. Although statistical studies may suggest certain relationships, the high incidence of these discharges in a normal population makes evaluation in any given patient exceedingly difficult.

Normal Electroencephalograms

Electroencephalographers know that patients subject to unquestionable seizures may have normal electroencephalograms. Clinicians often feel vexed and frustrated by such reports. Obviously, the patient is not normal. How can his electroencephalogram be normal? Probably several factors account for this seeming paradox. As we mentioned previously, even a prolonged recording period of two hours constitutes less than 10 per cent of the day. Thus, in a sense, the examination becomes a sampling procedure in which we attempt to extrapolate from 10 per cent of the potential data. Viewed in this light, the electroencephalogram astonishes one by its reliability. One can, of course, increase the likelihood of detecting abnormality by increasing the size of the sample. Since prolonging the period of recording is usually impractical, repeated examinations often constitute a solution. At other times exploiting the diurnal cycles of seizures may help. For example, myoclonic seizures typically occur in the morning shortly after awakening. We have observed instances in which the electroencephalogram of a patient with myoclonus showed typical bursts of multiple spike and wave discharges in the early morning but was normal in the afternoon.

Prior administration of anticonvulsant drugs may be another factor. As we have explained, the likelihood of precipitating seizures constitutes too great a risk to justify routinely discontinuing drugs. We occasionally do stop medicine under careful supervision, but each such case must be decided on its own merits. Nevertheless, the reader should remember that anticonvulsant drugs may suppress all abnormality in the electroencephalogram while still not entirely eliminating the patient's seizures.

In recent years electroencephalographers have learned that the electroencephalogram, as it is detected on the scalp, gives only a fragmentary picture of the electrical activity of the brain. Reason tells us that the relative remoteness of many nuclear masses, for example amygdala or thalamus, should render them inaccessible to scalp electrodes. Electrodes inserted through the nose or beneath the sphenoid bone have made some of these regions accessible with relative ease. The introduction of techniques for intracerebral implantation of electrodes has greatly broadened the scope of our knowledge. Depth electrography has shown that violent electrical storms may sweep the depths while the surface remains unruffled. Thus, a normal interictal recording from the scalp does not preclude the simultaneous appearance of undetected epileptiform discharge in the depths.

TECHNIQUES FOR ACTIVATION

Electroencephalographers have sought a simple and reliable method for evocation of latent abnormalities. Such a goal has yet to be attained; however, certain methods of "activation" of abnormality offer varying degrees of usefulness.

Hyperventilation

Neurologists have long known that hyperventilation can sometimes precipitate seizures in epileptic patients. Children with petit mal seizures are the group most responsive to hyperventilation; however, less commonly, overbreathing may provoke any type of seizure. Electroencephalographers adopted the technique and soon learned that in many instances changes appeared in the electroencephalogram even in the absence of clinical symptoms. Consequently, overbreathing has become a standard part of the electroencephalographic examination.

The patient is asked to overbreathe forcefully for about three minutes, after which he is told to resume a normal rate of breathing. Even relatively young children can cooperate in this maneuver. Changes in the electroencephalogram, in general consisting of diffuse slowing, regularly occur in children. The slowing disappears within a minute after the cessation of overbreathing. In a smaller percentage of adults and aged persons comparable changes appear. These changes may be aggravated by mild hypoglycemia, such as that induced by fasting overnight. For this reason, electroencephalographers generally prefer to avoid examining patients in a fasting state.

Hyperventilation may convert a normal record into an abnormal one by evoking any of the previously described abnormalities. The abnormal discharges may persist for some minutes after the cessation of overbreathing. Occasionally the increasing abnormal discharges may culminate in a seizure. Rather commonly hyperventilation accentuates existing abnormality, either by augmentation of voltage or by greater persistence. Bisynchronous rhythmic abnormalities seem particularly responsive to overbreathing. Originally it was thought that hyperventilation produced its action by alterations in the pH of the blood. Current theory holds that the action is due to alterations in cerebral blood flow consequent to a fall in pCO_2.[8]

Photic Stimulation

In the past, occasional patients were reported whose seizures seemingly were precipitated by flickering light. Time has proved the validity of this observation, resulting in a considerable literature devoted to patients whose seizures can be precipitated by such means. Electroencephalographers quickly adapted this observation to the laboratory, developing procedures for exposing the patients to rhythmically flickering lights. In some patients both abnormal discharges in the electroencephalogram and clinical seizures can result; in others only electrographic changes appear.[2] Experience has shown that patients most sensitive to light are those whose seizures appear to arise subcortically.

Here again, the procedure is a simple one, and we employ it in the examination of all patients with seizures or suspected seizures. The patient is subjected to rhythmically flashing lights at frequencies varying between 1 and 20 cycles per second. Stimulation is done when the patient's eyes are open and again when they are closed. In normal persons this procedure may evoke from the occipital regions responses which follow the flash rate (photic driving). Although the number of light-sensitive epileptics is small, we believe the procedure should be a regular part of the examination of all epileptic patients.

Pharmacologic Methods

Over the years many drugs have been employed in attempts to provoke abnormality in the electroencephalogram. The ideal drug would consistently reproduce a typical attack in an epileptic patient but would have no effect on a normal person. By the same token, the drug would cause no change in the electroencephalograms of normal persons but would evoke the abnormality peculiar to each epileptic patient. We do now know of any drug possessing such properties.

Pentamethylentetrazol (Metrazol) has attracted more interest than most drugs,[1] although at the present time it commands less attention than it did a few years ago. Unquestionably, it can at times evoke a patient's typical seizure. However, in persons not normally subject to seizures, it can provoke not only changes in the electroencephalogram but generalized convulsions. We do not find it very helpful in clarifying the diagnosis of clinically vague cases.

In sum, we believe that pharmacologic methods have not yet evolved to a level of reliability and consistency commensurate with clinical demands. For this reason, we only occasionally utilize such methods in attempts to "activate" the electroencephalogram. Pentamethylentetrazol seems more useful for provoking attacks in known epileptics, thus permitting precise analysis of the pattern of the seizure under controlled conditions. Less often does it establish unequivocally the diagnosis of epilepsy in a patient with obscure symptoms.

ADVANCED TECHNIQUES

We have already alluded to intracerebral implantation of electrodes.

The intent of this procedure is to permit intensive study of a patient with focal seizures prior to surgical intervention for attempted removal of an epileptogenic area. At the present time, direct recordings from the surface of the brain at the time of craniotomy (electrocorticography) and implantation of depth electrodes remain advanced procedures, best carried out in specialized centers dedicated to the care of epileptic patients. Their usefulness will necessarily remain limited since the number of patients who are potential candidates for surgery is extremely small.

ELECTROENCEPHALOGRAPHY AND DRUG THERAPY

Electroencephalographers are often asked about the relationship between electroencephalographic abnormalities and clinical response to drug therapy. The type of abnormality in the electroencephalogram offers no clue as to which drug should be employed. Similarly, the electroencephalogram taken while the patient is under treatment does not predict reliably the effect of drugs in controlling seizures. In some patients the electroencephalogram may remain grossly abnormal although the patient is free of attacks. Conversely, seizures may persist even when the electroencephalogram has reverted to normal. We believe that repeated electroencephalograms offer little assistance in evaluating the program of drug therapy.

With a patient who has not had seizures for two or three years, clinicians may call upon the electroencephalographer to aid in deciding upon termination of drug therapy. Often no unequivocal opinion can be given. In general, we favor continuing treatment of patients whose records remain strikingly abnormal since we believe that such persons have a greater likelihood of attacks. Conversely, if the electroencephalogram is normal, we will consider withdrawal of drugs. If the electroencephalogram shows reversion to gross abnormality following withdrawal, we may then reconsider the decision and resume drug administration. However, we would caution against overdependence upon the electroencephalogram to the exclusion of clinical factors.

SUMMARY

We have attempted to review electroencephalography from the viewpoint of the practitioner using it as an aid in the clinical evaluation of patients with seizures or suspected seizures. Epilepsy is not a disease but a symptom-complex resulting from many diverse causes. Just as there is no single cause of epilepsy, there is no electrical sign peculiar to epilepsy. For this reason, we have emphasized strongly that epilepsy must be diagnosed on clinical grounds and not from the results of any laboratory examination. Nevertheless, electroencephalography is prob-

ably the most valuable laboratory test in the evaluation of seizures, offering information as to the locus of abnormal discharges and, occasionally, clues to the underlying causes.

We have reviewed the normal electroencephalogram and its maturational changes. Although seizures have no pathognomonic electrical abnormality, certain types of discharges occur with great frequency in epileptic patients. However, even such "epileptiform" activity may appear occasionally in patients without known seizures. Other, "nonspecific" abnormalities occur not only in patients with seizures but in many other patients not subject to seizures. A few patients with seizures may have no abnormalities in the interictal recordings. Since in some patients abnormal discharges arise only when they are asleep, recordings during sleep may be essential.

We have reviewed procedures for evocation of latent abnormality. Hyperventilation and photic stimulation should be a part of the routine examination. Pharmacologic activation may occasionally be helpful.

We have discussed the electroencephalogram in relation to drug therapy, cautioning against overdependence upon the electroencephalogram and underdependence upon clinical judgment.

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Neuroradiological Aspects of Epilepsy

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INTRODUCTION

It should be appreciated that there is no specific roentgen finding or group of findings that will enable one unequivocally to diagnose epilepsy. This applies not only to plain skull examinations but also to special studies such as pneumoencephalograms, ventriculograms and cerebral arteriograms. There are, however, various manifestations and abnormalities that are found by roentgenographic examination that can correlate with and substantiate a carefully recorded history and clinical findings. Likewise, the x-ray study can serve in the over-all evaluation of a patient when viewed with the knowledge of: family and personal history, physical examination, examination of the cerebrospinal fluid, characteristics of the seizure pattern, and results of electroencephalography. Not infrequently a convulsive disorder is tentatively diagnosed as idiopathic epilepsy following the initial history and physical examination, but often after a complete work-up the diagnosis is modified because the radiographic examinations reveal significant lesions. This indicates the necessity for complete and adequate evaluation of all patients for whom this diagnosis is given consideration. Convulsive disorders that commence after the third decade of life usually have an underlying organic basis and certainly should arouse suspicion leading to a complete evaluation.

Roentgenographically, there are two broad types of focal epilepsy: (1) that associated with demonstrable cerebral lesions, including expanding lesions, cerebral cicatrix, local cerebral atrophy, local microgyria, brain cyst, diffuse cerebral disease, diffuse cerebral vascular disease, and a miscellaneous group including congenital lesions; (2) that in which there are no demonstrable lesions, such as epilepsy following toxic and febrile reactions, and idiopathic or familial types.[24]

Generally it is considered that patients with infratentorial expanding lesions rarely have concomitant focal epilepsy.[24] Convulsive disorders also are relatively infrequent concomitants of lesions of the pituitary, basal ganglia or thalamus. The closer the cerebral lesion is to the fissure of Rolando, the greater the possibility of generalized seizures. Seizure activity is more frequent with lesions in the frontal, temporal and parietal lobes than in the occipital area.

A simple atrophic lesion indicates only that one of the structures of the brain and its contents are involved. It may result from arterial occlusion with complete disappearance of brain tissue in a localized area, or thrombosis of a cortical vein may result in focal atrophy. Cerebral hemorrhage in its early stage may produce a similar pathologic result. Trauma also has been implicated in such localized atrophic lesions.

ROENTGENOGRAPHIC EXAMINATION OF THE SKULL

In an adequate diagnostic work-up of a patient in whom epilepsy is a consideration, x-ray examination of the skull is mandatory.[3] This includes posterior-anterior and lateral stereoscopic films and an occipital view as the minimum. Depending upon the correlation of the findings on the plain skull films, the clinical data and the electroencephalographic report, special studies such as a pneumoencephalogram, a ventriculogram and/or a cerebral arteriogram can be considered.

Plain skull films may be entirely normal. However, if patients have suffered from brain damage at birth or during the first year of life, or if older patients have sustained head trauma, significant alterations may be appreciated on the routine skull examination. If patients have experienced severe brain damage at birth, the skull may well be small, with premature closure of the sutures resulting in microcephaly.

Interesting and significant abnormalities are demonstrated in those individuals who have suffered primarily unilateral brain damage. The most common roentgenographic finding in atrophic lesions of the brain causing focal epilepsy has been cranial hemiatrophy, which is present in approximately one half of these patients.[18] One side of the cranial vault may be smaller when the corresponding cerebral hemisphere is underdeveloped or hypoplastic (Fig. 1). The contralateral arm and leg likewise may be small as a concomitant manifestation when the postcentral gyrus is involved. The reduction in volume of one lateral aspect of the skull is probably the most important finding. However, the degree of asymmetry cannot and should not be assumed to have a direct correlation with the extent of the brain injury.[18] On the underdeveloped side the parietal bone and the temporal squamosa are often thickened. The ethmoid and frontal sinuses may be enlarged on the hypoplastic side. One must realize, however, that the frontal sinus in normal persons can exhibit a moderate to large degree of asymmetry, so that this finding alone should not be considered significant. The mastoid air cells are another area in which the asymmetry may be distinct, with overdevelopment on the small side of the cranial vault. Varying degrees of elevation and smoothness of the ipsilateral petrous ridge can be additional plain film skull manifestations. Decreasing in incidence and significance is the occasionally noted displacement of the groove for the superior longitudinal sinus to one side of the sagittal suture and the possible elevation of the orbit in the involved hemicranium.

The presence or absence of cerebral hemiatrophy is generally directly related to the age of the patient at the onset of this type of focal epilepsy. It is an accepted fact that the maximal growth of the central nervous system occurs during the first two years of life; the most pronounced degree of cranial atrophy (restricted to one side as a concomitant finding with cerebral hemiatrophy) is demonstrated in those patients whose disease dates to this early period of development. After the age of two until the age of puberty there is very little brain growth, and though hemiatrophy can develop it is far less significant. It is important to remember that these combined and interrelated manifestations of hemiatrophy do not follow brain damage which originates in later life. These phenomena, therefore, are changes resulting from the lack of the stimulus of a normally growing and developing brain beneath the involved side of the skull. In viewing the skull films, it is extremely important to realize that mild apparent cranial asymmetry can be produced by slight

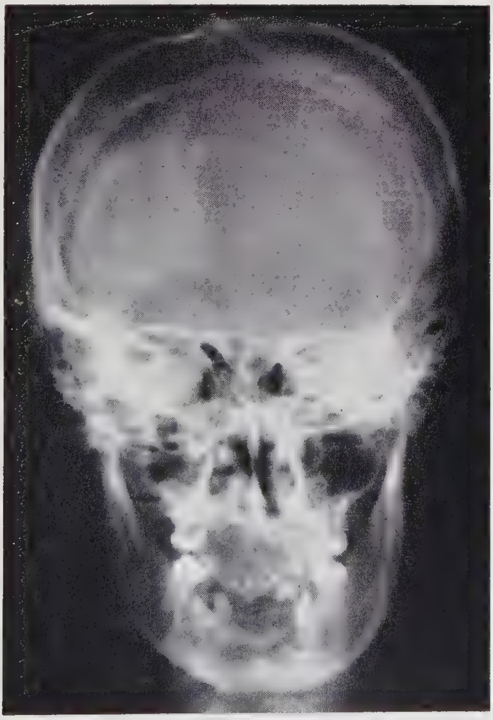


Fig. 1. Right cranial hemiatrophy. Posteroanterior skull roentgenogram. Distinct enlargement of the right frontal sinus and mastoid air cells with associated underdevelopment of the right cranial vault.

rotation of the head at the time of filming. Minor degrees of asymmetry of the cranial vault may not be recognized unless viewed stereoscopically or unless tracings of the contours of each half of the skull are made and compared. Occasionally asymmetry may not be demonstrated even when there is definite cerebral hypoplasia because compensation is made entirely by ventricular dilatation.

HEAD INJURIES

Cranial fractures occurring early in life usually heal rapidly and completely, even to the extent that a depressed fracture may not be evident in subsequent years. In older people, fractures heal more slowly but most of them likewise tend to disappear. However, when the dura is interposed between the edges of the bone at the fracture site, the fracture often remains open and may persist into later life. A depressed skull fracture may reveal the bony fragments to be either attached to the adjacent nondepressed bone, or possibly situated deeply within the cerebral or cerebellar tissues. Cases involving major head trauma (i.e., war injuries, industrial accidents, etc.), are apt to demonstrate intracranial foreign material: metal fragments, glass, plaster, hair, bricks, wood and other debris. These significantly predispose to the development of epilepsy.

Following head injury, there may be a deficiency or local absence of the dura. This leaves the brain in direct contact with the inner table of the skull, inducing demonstrable bony changes. Because of the pressure of pulsating brain tissue against the bone, there may be either erosion (sometimes with the formation of small depressions) or new bone formation (Fig. 2). With head trauma there may be involvement of the brain, the dura or the bony calvarium in combination or individually. When the brain substance and the dura are damaged at the same point, a meningocerebral cicatrix will form. At such a site, the subdural adhesions are often thick and tough and may even penetrate the brain to the level of the lateral ventricle. The demonstration of the presence of such a cicatrix will often direct attention to this site as an epileptogenic focus. Meningocerebral cicatrices have no age predilection; the only predisposing factor is head injury. It is important to realize that these scars contain no nerve cells; therefore, they themselves do not cause the seizures.

In association with a meningocerebral cicatrix there may be localized bony defects from old fractures or from previous surgery. The cicatrix itself is capable of leading to craniocerebral erosion or a localized thinning, with possible bulging, of the bone in approximately two thirds of the patients with this pathologic condition (Figs. 3 and 4). Underdevelopment of one hemicranium with ipsilateral bone thickening can occur with a meningocerebral cicatrix, as seen in a simple atrophic lesion. One

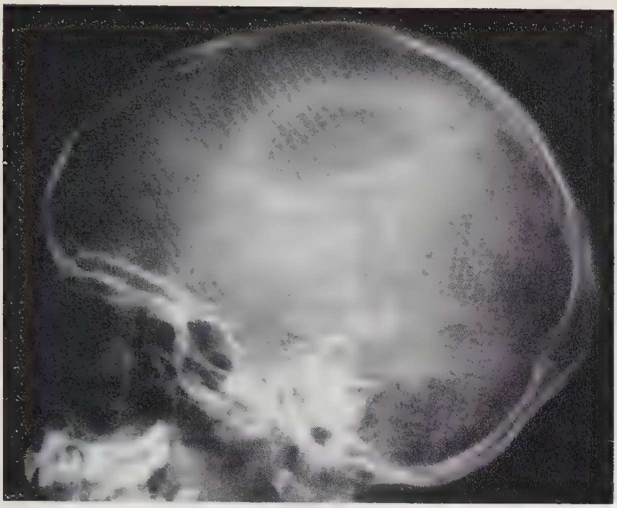


Fig. 2. Meningocerebral cicatrix with craniocerebral erosion in a 5-year-old girl following head injury at 3 weeks of age. Lateral skull roentgenogram. Presence of an oval defect in the parietal area with smooth but wavy margins. A fracture line extends upward and backward from the posterior edge of the bone defect. Along the anterior edge there is some evidence of erosion and sclerosis.

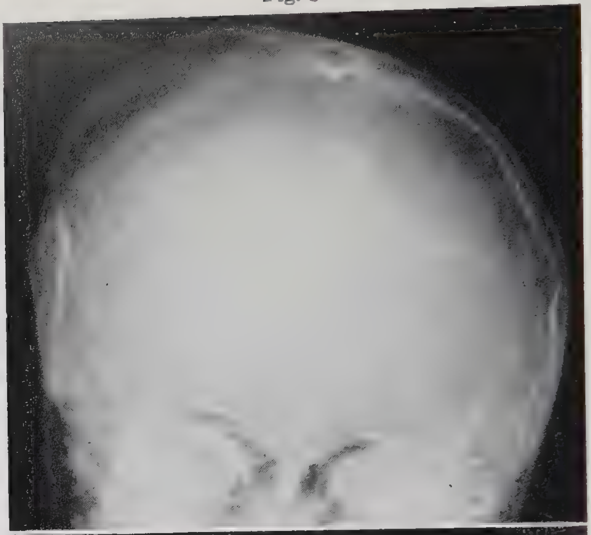
cannot always differentiate, therefore, the underlying factor for a demonstrable hemiatrophy. The status of the sinuses, petrous ridges and mastoids may be of no assistance in this differential. An analysis by McRae of atrophic lesions that contract, subsequently causing epilepsy, revealed meningocerebral cicatrices to be the most prevalent.[18] The relative incidence of bony changes in association with meningocerebral cicatrix is six times greater than that with other lesions producing epilepsy.[18] The incidence in patients seen with meningocerebral cicatrices is significantly higher in males because of the nature of their occupations, hazards of life and economic responsibilities. The average age in one series of those seeking medical attention because of this disorder was 22.4 years.[18]

Physiologic and Pathologic Intracranial Calcification

Another important observation to be made on plain skull films is the possible demonstration of vascular calcification or physiologic calcification of intracranial structures. Calcification of internal carotid arteries indicates intracranial arteriosclerosis. Abnormal position of the calcified pineal or displacement of a calcified choroid plexus may signify either an expanding or a contracting lesion.

Degenerative atrophic lesions that may calcify and be visible on routine roentgen studies and that have been incriminated as etiologic agents for epilepsy include toxoplasmosis, tuberous sclerosis and cysti-

Fig. 3



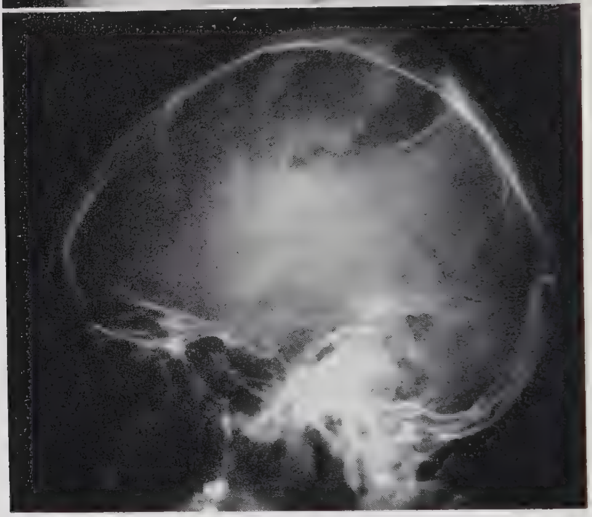


Fig. 4

Fig. 3. Meningocerebral cicatrix in a 14-year-old boy with right parietal bulging following skull fracture at 3 months of age. Posteroanterior skull roentgenogram. Focal seizures have been present since the injury. Marked thinning in the posterior parietal area in association with the bulging deformity.

Fig. 4. Same patient as Fig. 3. Lateral skull roentgenogram. Meningocerebral cicatrix with craniocerebral erosion in association with bulging of the posterior parietal region.

cercosis (primarily in veterans who have been on overseas duty or those who have lived in India).[26] Superficial calcification and even ossification from old subdural hematomas are not infrequently observed. When such a pathologic process is demonstrable and is found in association with epilepsy, there is good indication of associated brain damage.[24] Old cerebral hematomas occasionally show areas of localized calcification.

As will be noted in the next section, intracranial calcification can occur in a vascular abnormality. If a pathologic intracranial calcified area is noted in a patient with focal epilepsy, and gliomas or meningiomas can be excluded, the chance that it is a vascular lesion rather than some other degenerative type is approximately fifteen to one.[18] Plain skull films of adults with recent onset of seizure activity may reveal distinctive calcification in the more slowly growing brain tumors. Follow-up films in difficult cases may reveal the subsequent development of calcification in tumors or cysts.

VASCULAR MALFORMATIONS

The third largest group of patients with focal epilepsy are those with vascular malformations of the brain. Occasionally atrophy may be an associated finding, but more common is the presence of small intracranial calcifications in the region of a vascular anomaly or hemangioma. In some cases of Sturge-Weber syndrome there are demonstrable facial nevi, focal seizures, electroencephalographic changes and ocular abnormalities. The usual manifestation is for the focal seizures to be contralateral to the facial nevus. Particularly in these patients there will be no significant change in the cerebral calcification over an extended period. In this particular subgroup, angiography is noninformative except to rule out the presence of other blood vessel malformation.[14]

EXPANDING LESIONS

Expanding lesions, such as tumors, may develop in patients with or without previous head trauma. Many neoplastic processes, primary or metastatic, though small, located in a strategic area can produce epilepsy. A mass lesion is much more likely to produce or be associated with focal seizures than with generalized seizure activity. Intracranial tumors of infancy and childhood, because of their usual location in the cerebellar hemispheres or posterior fossa, do not often cause seizures. One should always give strong consideration to a tumor when epilepsy commences in adult life, particularly after the third decade. This is especially true when no other obvious cause can be confirmed. Such tumors may calcify and be localized on plain skull films. Frequently convulsive disorders are the initial symptom of a brain tumor and may lead to a premature and erroneous diagnosis of epilepsy. This pitfall is accentuated by the fact that the neurologic examination may initially be negative. Only with an index of suspicion, therefore, may one consider a brain tumor in the presence of seizure activity. In one of the excellent articles by Penfield and associates dealing with focal epilepsy, the incidence of focal seizures associated with expanding lesions above the tentorium was lowest among the more malignant lesions (37 per cent in glioblastoma multiforme), whereas the incidence was highest among the more slowly growing intracranial lesions, such as oligodendroglioma (92 per cent).[24]

PNEUMOENCEPHALOGRAPHY

For an adequate and complete evaluation of an epileptic or a patient in whom the diagnosis is given strong consideration, pneumoencephalography and/or contrast opacification of intracranial vascular structures are indicated. Many physicians feel that no patient with focal epilepsy has been studied completely until an air study has been performed. In the absence of increased intracranial pressure a pneumoencephalogram is the method of choice. This is an important factor in attempting to secure visualization of the subarachnoid spaces. This discussion does not warrant evaluation or description of the surgical or roentgen techniques of these various special procedures; however, the pertinent roentgen manifestations will be reviewed. Basically, one has to admit that there has been no definite set of measurements or standards acceptable to all for the size and shape of the normal ventricle.[9] Generally accepted is the premise that the lateral ventricles are small in normal young persons and that they increase in size from the age of 25 until 60. Fortunately this normal increase in size as a manifestation of age bears no significant or direct relationship to mental capacity. A significant percentage of patients with focal epilepsy reveal no abnormality that can be seen with the best possible visualization and excellent radiographic techniques. Small expanding lesions such as neoplasms and focal atrophic lesions (especially small closed cysts) may produce no appreciable deformity upon the gas-filled ventricular system. Nevertheless, when the pneumoencephalogram is normal the probability is that an exploratory craniotomy would also be negative.

Generally pneumoencephalography is a valuable and relatively safe procedure in the over-all evaluation of an epileptic patient.[6] One must again emphasize the fact that there are no specific lesions characteristic of epilepsy that might be revealed on a pneumoencephalogram.[6] Changes appreciated on such a study in an epileptic patient may also be seen in a nonepileptic. Therefore, the changes that are manifest are not an essential component of a convulsive disease, but are the result of the process that underlies the disorder or only an associated finding. Not infrequently special studies of this type elicit lesions that have not been suspected from history and physical examination. To some degree unrewarding, but informative, is the fact that upon pneumoencephalography the presence of irreversible changes may be confirmed; thereby, the general prognosis of a specific individual may be established. In earlier literature the therapeutic value of a pneumoencephalogram was occasionally suggested; this has since been proved to be erroneous.

Localized enlargement of a portion of the lateral ventricle is significant. Such focal enlargement may be found in a person who does not have epilepsy; but if he does have focal seizures, the lesion which is responsible is often somewhere in the vicinity of that portion of the lateral ventricle which is most markedly dilated. Very often, the causative lesion is in the cortex of the brain directly superficial to a point of maximal enlargement of the ventricle. Frequently a considerable portion of one lateral ventricle is enlarged, and occasionally the entire ventricle may be uniformly enlarged (Fig. 6). When this occurs the focus can be lateralized but otherwise not specifically localized. Following injuries or vascular accidents, extreme localized enlargement of a portion of the lateral ventricle may occur with disappearance of most of the overlying brain, especially in the occipital region (Figs. 5 and 7). In these cases the epileptic focus is at the periphery of the area of major atrophy and not over the destroyed area. Temporal lobe epilepsy often reveals distinctly dilated sulci and wide temporal horns[9] (Figs. 8 and 9).

In one reported series approximately 80 per cent of the patients with meningocerebral cicatrix had focal ventricular dilatation, demonstrable subarachnoid cysts being formed in approximately 18 per cent.[18] Focal ventricular enlargement or dilatation was present in 38 per cent of patients with simple atrophic lesions and there was an associated 5 per cent incidence of subarachnoid cysts.[18]

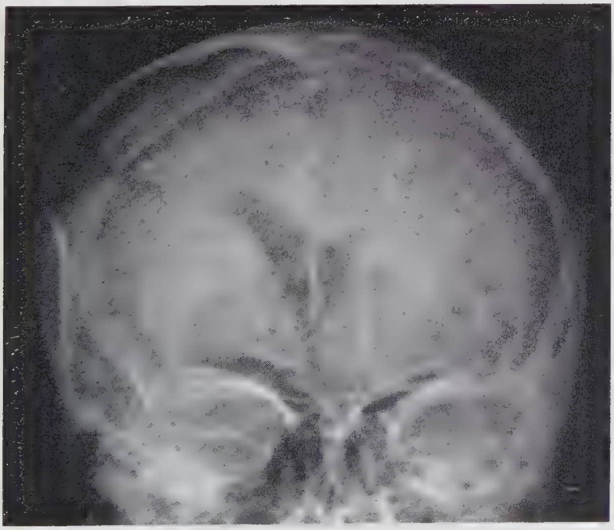


Fig. 5. Same patient as Figures 3 and 4. Posteroanterior encephalogram. The septum pellucidum is in the midline and the left lateral ventricle appears normal. The right lateral ventricle is dilated and pulled upward and outward toward the bony defect in the parietal area. The enlargement is most prominent immediately beneath the area of bone deficit. Some of the subarachnoid channels immediately beneath the right parietal bone defect are dilated.

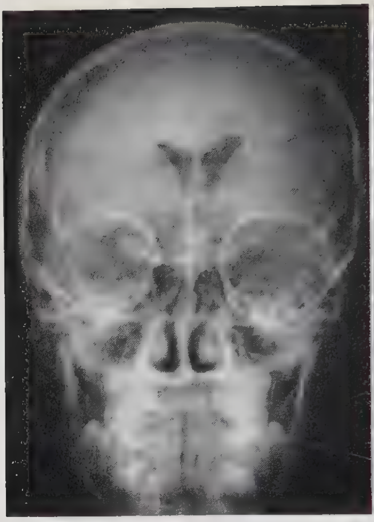


Fig. 6

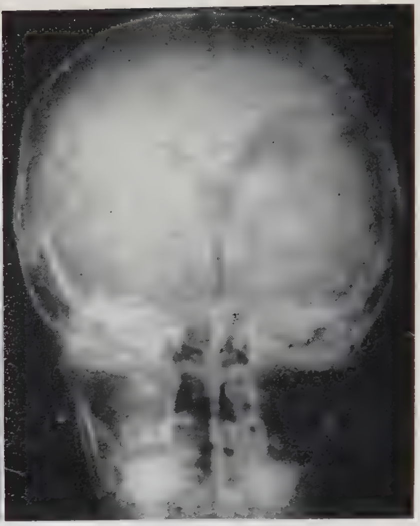


Fig. 7

Fig. 6. Unilateral left cerebral atrophy. Anteroposterior encephalogram. Slight shift of the ventricular system to the left. Generalized dilatation of the left lateral ventricle in association with a slight shift indicating left cerebral atrophy.

Fig. 7. Same patient as in Figure 2. Recumbent posteroanterior encephalogram. Right lateral ventricle is of normal size. There is focal dilatation of the left ventricle immediately beneath the defect in the parietal bone. Large gas-filled subarachnoid spaces are localized beneath the area of bony alteration indicating a loss of brain substance. Generalized shift of the midline structures toward the left, but the ventricular enlargement is confined mainly to the area adjacent to the bony lesions.

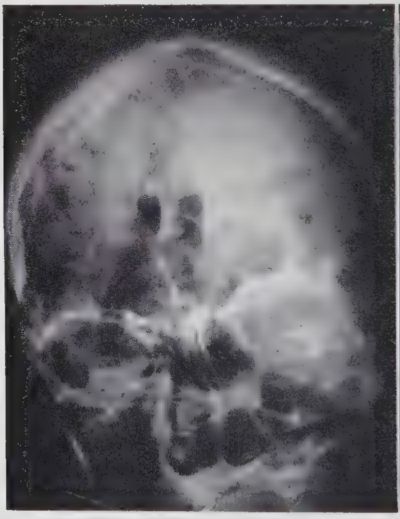


Fig. 8

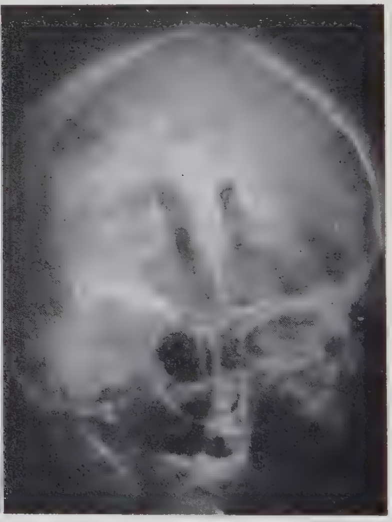


Fig. 9

Fig. 8. Encephalographic right temporal horn view. The temporal horn of the right lateral ventricle is generous in size and wider than the contralateral temporal horn.

Fig. 9. Encephalographic left temporal horn view. Same patient as Figure 8. The temporal horn of the left lateral ventricle is normal.

Porencephaly, a cavity within the brain, is often associated with convulsive disorders. This condition may be the result of vascular, inflammatory or traumatic processes during fetal life. Some observers believe it to be a congenital malformation or even one based on a germ plasm defect. Trauma, in either fetal or adult life, is the most common cause, however. The cavity may communicate with the lateral ventricle or the subarachnoid space either by generalized enlargement of these structures or by a narrow neck (Figs. 10 and 11). Porencephaly is most frequently located in the distribution of the middle cerebral artery. Delayed films in a pneumoencephalogram are extremely important in attempting to visualize areas of porencephaly.

At times the ventricles are comparatively normal but there can be enlarged subarachnoid spaces localized over the cerebral hemisphere near an epileptic focus. Local puddling of excessive amounts of gas signifies loss of brain substance, and below the age of 40 dilated sulci are pathologic.

In the presence of a localized deformity of a lateral ventricle and/or alterations in the subarachnoid space (in association with clinical localizing correlation), surgical removal of the focus is the most rewarding procedure in an effort to control the seizures. There is a slight relative increase in positive pneumoencephalographic findings and correlation

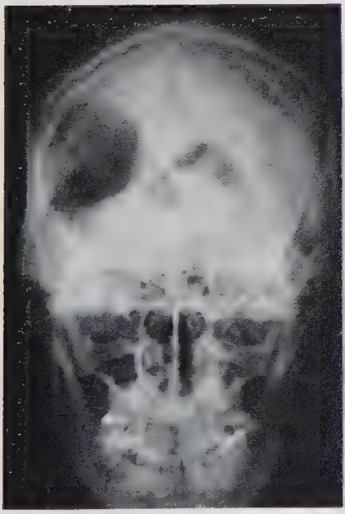


Fig. 10

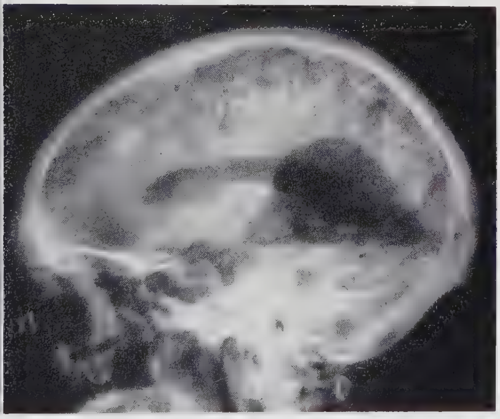


Fig. 11

Fig. 10. Porencephaly. Posteroanterior encephalogram. 37-year-old patient with seizures since the age of 10 years. Note smooth inward depression of right temporal squamosa where the bone is unusually thick. Pneumoencephalogram reveals right cerebral hemiatrophy, generalized dilatation of right lateral ventricle, and large gas-filled porencephalic cavity in the region of the right parietal, temporal and occipital lobes.

Fig. 11. Porencephaly. Lateral upright encephalogram. Same patient as Figure 10. Large cavity with air-fluid level in right parietal, temporal and occipital lobe.

with focal seizure activity in meningocerebral cicatrix over those in simply atrophy. Occasionally, positive x-ray findings point to a lesion of the opposite hemisphere from that of the otherwise localized epileptogenic focus. This would suggest that the lesion demonstrated by roentgenographic means is larger than the epileptogenic focus. Rarely, bilateral plain skull abnormalities and/or ventricular abnormalities are demonstrated with a unilateral epileptogenic focus. The frequency of seizure activity is not related to the demonstration of atrophy by pneumoencephalogram. Because of the uncertainty of the normal limits of an encephalogram, the pathologic importance of minor dilatation of either of the lateral ventricles or sulci is undetermined. In one series of post-traumatic cases, almost half the patients with generalized seizures following closed head injury had normal air studies, while less than a third of those with focal seizures following closed head injury had normal pneumoencephalograms.[26] It should be noted that in cases of idiopathic epilepsy pneumoencephalograms can be normal. However, with repeated grand mal attacks through the years there may be cerebral degeneration, revealing on the pneumoencephalogram diffuse cerebral atrophy.[5] This has been postulated to be caused by anoxia. Repeated episodes of status epilepticus lead to more pronounced cerebral damage. Other authors believe the converse, that there is no definite evidence that dilated ventricles are related to chronologic age, duration of the disorder or frequency of the attacks.[9, 15]

Pneumoencephalography can often reveal space-occupying lesions such as tumors, which may serve as foci for epilepsy. Actually the epileptogenic focus lies in the transition zone between the tumor and normal brain tissue. The nerve cells in the zone of transition are still viable but are in an altered environment and act in a different and abnormal manner. Tumors in an adult without positive history of previous head injury very frequently lead to epilepsy of the focal or generalized type. Space-occupying lesions can cause distortion or displacement of or encroachment upon the air-filled ventricular system which can often be demonstrated. This is manifest by deformities in the outline of the adjacent ventricle or a shift of the ventricular system away from the tumor. When the third ventricle is involved there may be an absence of filling of either the entire space or only a portion of it. If the lesion is large enough to obstruct the lateral ventricles at the foramina of Monro there will be bilateral and often symmetrical enlargement of the lateral ventricles. Likewise, tumors of the cerebellum and adjacent structures in the posterior fossa will result in a dilated third ventricle and symmetrical dilatation of the lateral ventricles. When a tumor is present within a lateral ventricle, a localized space-occupying defect within the ventricular cavity will be visualized along with a shift of the ventricle away from the mass. The pneumoencephalogram may be normal early in the development of the tumor, but the neoplasm may be demonstrable by this method of examination at a later date. A normal study does not completely exclude the possibility of a small underlying space-occupying lesion such as a tumor.

There may be associated seizures early in the course of brain abscesses in approximately one-half of the patients. During this early phase, a brain abscess is revealed as a space-occupying lesion. The seizure activity usually disappears soon and is by no means a constant concomitant finding. Months or usually years later, seizures may appear or reappear and a pneumoencephalogram usually shows general ventricular dilatation in the area of the original abscess. An associated finding may be the obliteration of adjacent subarachnoid spaces.

Generally air studies are of little benefit for securing additional information when repeated at selected intervals. That is, they have very little prognostic value once a diagnosis is established. However, if a patient's general condition changes, a repeat study should be considered.

ARTERIOGRAPHY

Arteriograms often reveal hemangiomas or arteriovenous malformations even though the plain skull films may have been negative. Arteriog-

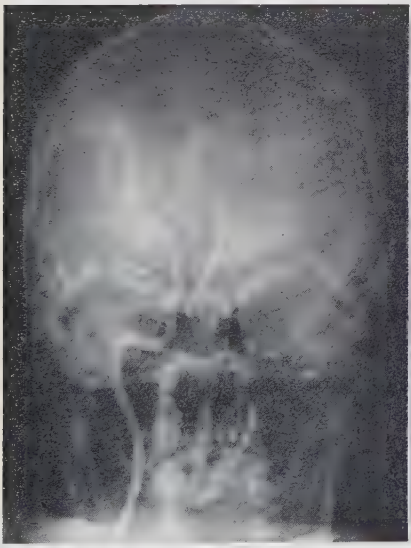


Fig. 12

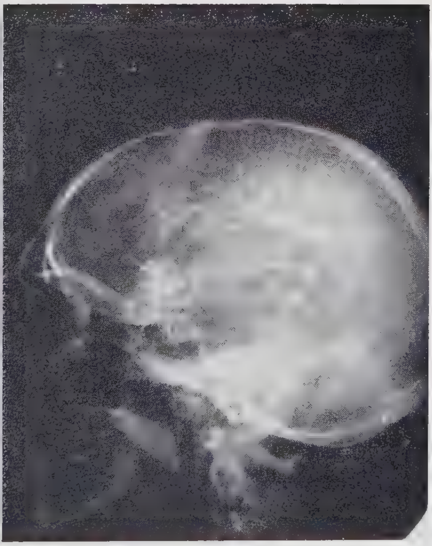


Fig. 13

Fig. 12. Glioblastoma multiforme. Anteroposterior cerebral arteriogram. Displacement of midline anterior cerebral artery to the left. Marked elevation and inward stretching of the right middle cerebral artery by the right temporal lobe mass.

Fig. 13. Glioblastoma multiforme. Same patient as Figure 12 . Lateral cerebral arteriogram. Abnormal circulation within the temporal lobe neoplasm demonstrated by opacification of characteristic multiple irregular vascular dilatations indicative of small arteriovenous communications.

raphic contrast studies also are of adjunctive aid in the diagnosis of tumors, either primary or metastatic, and subdural hematomas. In the presence of such space-occupying lesions one finds again stretching, displacement or distortion of normal arterial and venous structures of the intracranial circulation. A tumor may be identified on the arteriogram specifically by either displacement of the opacified vessels by the lesion or by the demonstration of an abnormal vascular pattern within the tumor. When pneumoencephalography is either unsatisfactory or contraindicated, carotid arteriograms are often very informative in both locating intracranial neoplasms and in giving some indication as to the histology.

DISCUSSION

One must appreciate that the over-all incidence of abnormal roentgen findings as well as the magnitude of the alterations will be decreased in noninstitutionalized patients with epilepsy. The merits of roentgen examinations in the evaluation of epilepsy and the incidence of positive correlation vary greatly in reports given in the recent literature. A significant degree of this discrepancy is undoubtedly due to the selection of the patients, the amount of clinical and electroencephalographic correlation, the authors' interest in epilepsy as a specific problem, the radiologists' interest and training as well as their personal criteria of normality as compared to abnormality. Interpretation of pneumoencephalograms, particularly with minor degrees of alterations, is often difficult; it is not uncommon to review films in the light of subsequent available clinical events and to see abnormalities previously missed.

SUMMARY

Although there are no specific roentgenologic changes diagnostic of focal epilepsy, certain abnormalities may correlate with the clinical evaluation and electroencephalographic findings to substantiate this diagnosis and possibly to permit an attempted surgical removal of the focus.

Patients with focal epilepsy may reveal the following roentgen alterations on plain skull examinations, listed in their order of frequency:

1. Cerebral and cranial hemiatrophy. Reduction in size of a lateral half of the skull is the most important finding on conventional roentgenograms;
2. Evidence of previous bone injury as a manifestation of trauma or of operative procedures;
3. Displacement of the calcified pineal, calcified falx or choroid plexus, usually toward the side of the cerebral atrophic lesion or away from a tumor;

4. The presence of abnormal calcifications, as in vascular malformations, tumors, degenerative or inflammatory lesions.

Special studies such as pneumoencephalograms or arteriograms may confirm the presence of either space-occupying or atrophic lesions. They also can be entirely normal in individuals with focal epilepsy.

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Management of the Epileptic Patient

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THE PATIENT with seizures presents to his physician two problems, the determination of the cause of the seizures and their management. These two problems are not mutually exclusive, for the etiology in an individual case will do much to shape the course of management.

The determination of the etiology of the seizures depends upon many factors including the family history, past history, age at onset, type of seizure or seizures, presence or absence of abnormal neurological findings, characteristics of the electroencephalogram, radiographic studies, and other laboratory findings. Seizures beginning before the age of 10 or after the age of 20 are usually due to a structural brain lesion. The same is true of seizures which have focal connotations in their clinical picture, of those appearing in patients with focal neurological disturbances, or of those for which the EEG shows a definitive focus rather than a generalized dysrhythmia. Seizures occurring in patients with a strongly positive family history, with an age at onset between 10 and 20, in whom the electroencephalographic discharge is completely generalized and in whom there are no abnormal neurological findings, are most apt to represent a type of epilepsy characterized as gentic, essential, centrencephalic or idiopathic.

CLASSIFICATION

The classification of seizure types is of obvious importance in arriving at a diagnosis of etiology and in choice of therapy. Among epileptologists there is no uniformly acceptable classification, but in the main the following seizure types and descriptions are acceptable.

Grand Mal Seizure

The classic seizure is the major convulsion, grand mal seizure or major motor seizure. This is characterized by the following sequence: A warning or aura, an involuntary cry, loss of consciousness, a tonic phase followed by a clonic phase with respiratory arrest and cyanosis. The seizure is usually followed by a period of unconsciousness, and urinary or rectal incontinence, seminal or vaginal emission frequently occur during the seizure. Upon regaining consciousness there is usually a period of headache and generalized muscle aches. During the seizure various traumas may occur to the patient ranging from tongue biting or lip biting to falls causing fractures, and even on rare occasions subdural or epidural hematomas. Three features of the clinical picture of a major motor seizure indicate that a seemingly generalized seizure actually has a focal point of origin. These three are: (a) a focal aura for example, auditory hallucinations; (b) a constant unilateral motor pattern at the onset of the seizure -for example, head-eye deviation always to the same side; and (c) focal deficit in the postictal phase following a single seizure—for example, aphasia, hemianopsia or weakness of a body part. Generalized motor seizures vary considerably in their incidence, some patients having only a single seizure every two or three years or even more infrequently, other patients having daily seizures. Usually, however, they vary between these extremes.

Petit Mal Seizure

Petit mal seizures occur in children with a frequency of more than one per day and last less than a minute individually. They are characterized by cessation of all activity and staring (absence), or single or few involuntary jerking movements (myoclonic), or a short period of unconsciousness and falling or dropping of an object (akinetic).[5] Hyperventilation will induce these seizures. They are uncommon after the age of 20 and rare after the age of 30 years.

Psychomotor Seizure

Psychomotor seizures or automatisms are due to temporal lobe discharges. They are characterized clinically by duration of more than a minute of psychic and/or motor activity, which is purposeful but irrelavent and for which the patient has an amnesia. These seizures often contain in their clinical picture involuntary lip and mouth movements with sucking and coughing noises. A classic example is that of the high school civics teacher who in an attack failed to rise at the playing of the National Anthem and instead remained seated and cursed audibly. At the end of the attack he had no idea of what had occurred.

Jacksonian Seizure

Jacksonian seizures are focal seizures, usually motor. They may rarely be exclusively sensory in type or mixed motor and sensory. These seizures begin in one part of the body and spread in a definite pattern to involve the entire extremity or face and then spread to other parts of the same side of the body. The three most common areas for the onset are the angle of the mouth, the thumb and the great toe. The motor component in Jacksonian seizures is clonic only. The sensory component is a peculiar paresthetic dysesthesia. The most significant characteristics of Jacksonian seizures are the clonic feature of the motor component, the definite march from the beginning point to a greater involvement of the part or even of the side, and the preservation of consciousness. Only when a Jacksonian seizure involves one entire side of the body and then spreads to involve the opposite side does loss of consciousness occur. This really is a generalized motor seizure with a focal motor (Jacksonian) onset, and of course has as much significance for localization factors as a pure and simple Jacksonian seizure.

Hallucinatory Seizure

Seizures arising from lesions in the special sensory cortex are often hallucinatory in type. The entire seizure may consist only of the hallucinatory seizure, or the hallucinatory episode may serve merely as an aura or beginning of a more severe seizure type such as a generalized motor attack. In a case of temporal lobe lesions, a hallucinatory episode frequently progresses into a psychomotor type of seizure. The special sensory hallucinatory seizures may be of the auditory, olfactory or visual type. The olfactory seizures (uncinate fits) are, strangely enough, almost always of a vile, unpleasant type. It is rare indeed for a patient with olfactory seizures to experience a pleasant odor. Auditory and visual hallucinatory episodes may be very simple, such as a buzzing in the ear or flashing of lights. They may be very complex, such as the first bars of a symphony production or complicated visual hallucinations. Occasionally auditory hallucinatory seizures are comprised of hearing certain words or phrases. Usually the patients find it difficult indeed to recall the exact nature of the words or phrases which they heard at the onset of their seizures. More complex memory patterns may also be evoked by seizure discharges. Penfield[8] has described highly complex situations, which the patient had experienced years before, occurring as this type of experience in the early stages of a seizure. Environmental clues also play a role in the seizure pattern.[3]

Seizure Evoked by Sensory Stimuli

Among the most interesting of all seizure types are those which are evoked by sensory stimuli, which may be auditory, visual or even somatosensory. Auditory evoked seizures include the more simple startle epilepsy; any sudden loud noise which occurs with an element of surprise will produce a seizure. A more complex type is that of musicogenic epilepsy;[4] the music of a particular composer or a particular instrument or a particular song will produce a seizure in the patient. Visually induced seizures have as their most common type that due to a flickering light.[2] The seizure is usually myoclonic but may be a truly generalized convulsion. The viewing of particular patterns or reading from a book will in some patients also produce seizures.[1]

ETIOLOGY

Seizures may be caused by virtually any disease of the central nervous system and by many systemic diseases. This of course complicates the management of the individual patient. Metabolic disorders involving the calcium or glucose metabolism are not common causes, but they must be considered as diagnostic possibilities. Because of the possibility of metabolic disorders, it is customary in children with seizures to obtain blood calcium and phosphorus levels and in both children and adults whose seizures occur only during the night or in the period between meals to obtain fasting blood sugars, prolonged (6 hours) glucose tolerance curves or 12- to 24-hour fasting blood sugar levels.

Cardiovascular diseases, especially those producing disturbances of heart rate or blood flow, may produce seizures. Stokes-Adams syndrome and carotid sinus hypersensitivity are examples. Fortunately, a careful history is a great help in leading to the proper diagnosis and clinical management of the metabolic and cardiovascular problems. For example, in the hypoglycemic patient seizures do not occur abruptly; the onset is gradual and in a particular relationship to the time of food intake. In carotid sinus hypersensitivity the seizures occur in the upright position and are associated with head movements.

However, the majority of seizures are due to cerebral disease. Atrophic lesions and brain tumors are the most common causes; abscesses, hematomas and vascular disease are less common ones.

SURGICAL MANAGEMENT

Surgical therapy is specifically indicated for those patients in whom the lesion causing the seizures is a brain tumor, brain abscess, subdural or epidural hematoma. Although seizures often are the first or only sign presenting in these patients, it is proper to consider that surgical therapy is mandatory for the disease and that the seizures are incidental. In this regard it is interesting to note that the first successful removal of a brain tumor in the United States was by Dr. W. W. Keene in 1888. The patient presented because of convulsions and the tumor was suspected because of the presence of seizures and an exostosis.

In patients with centrencephalic, genetic, essential or idiopathic epilepsy, surgical therapy is contraindicated. Some attempts have been made on an experimental basis to treat this type of patient by stereotaxic surgery directed at the thalamus, but this has not proved successful.

In patients with atrophic cortical lesions producing seizures, surgical therapy may be entertained as an elective approach. The criteria for the selection of the patient are that the seizures should be focal and reasonably consistent. The neurological findings should be in accord with the lesion of the area of cortex as indicated by the seizure pattern. The electroencephalographic evidence must be consistent on repeated testing. The x-ray evidence, including contrast studies, should be in accord with the clinical and EEG impression, and finally, the patient should be intractable to the appropriate medical therapy in adequate dosage. There are some instances of urgency in surgical selection. When, for example, following a Jacksonian seizure a patient has weakness of the extremity (Todd's paralysis) from which he regains most of the function but retains some persistent deficit, and following repeated seizures the persistent deficit becomes more and more pronounced, it is necessary to consider surgical therapy at an early stage. The same applies to the increasing mental deterioration which may occur after repeated major seizures of focal onset. When the most rigid criteria for selection are observed, the successful surgical removal of atrophic lesions produces somewhere between 50 and 60 per cent of complete recovery. When one works in a large epilepsy program, it becomes quite apparent that only a relatively small number of patients are acceptable for surgical therapy according to the criteria that have been described and that many patients can be successfully managed with proper and judicious use of newer medications.

MEDICAL THERAPY

Medications available at the present time for the treatment of epilepsy are the barbiturates, hydantoinates, oxazolidines, succinimides, primidones, and various miscellaneous preparations.

By and large the barbiturates tend to be very safe drugs. The most efficacious of all the barbiturates is phenobarbital. In relatively large doses it does produce drowsiness and in some patients blunting of intellectual productivity. Although mephobarbital (Mebaral) is less apt to produce this effect, it is usually necessary to give it in doses two to three times that of phenobarbital. Of the hydantoinates, sodium diphenylhydantoin (Dilantin) is the oldest and the safest; Mesantoin and Peganone are less likely to produce minor toxic signs, but Mesantoin is a dangerous drug. The oxazolidines (Tridione and Paradione) are effective drugs in the treatment of petit mal epilepsy but carry with them particular hazards. The succinimides, on the other hand, are quite free of untoward side effects. The earlier succinimides, Milontin and Celontin, were useful but did not present major advances in the treatment of

Table 1

	GRAND MAL	PETIT MAL	PSYCHOMOTOR	FOCAL
Barbiturates	++	+	++	++
Hydantoinates	++++	0	+++	+++
Succinimides	+	++++	+	−
Primidones	++++	−	++++	++++
Oxazolidines	0	++++	—	−

+ − ++++ = relative effectiveness, ++++ being most effective
0 = contraindicated
— = ineffective

Table 2

GRAND MAL SEIZURES	PETIT MAL SEIZURES	FOCAL SEIZURES
Phenobarbital	Phenobarbital	Mysoline
Dilantin	Zarontin	Phenobarbital
Mysoline	Tridione or Paradione	Dilantin
	Milontin	
	Celontin	

epilepsy; Zarontin, the newest member of the family, may be helpful in the treatment of petit mal epilepsy and indeed is sometimes effective in other types of seizures. The only primidone available is Mysoline, which causes some minor side effects of nausea and vomiting on the first dosage, thus precluding a further use of the drug. Drowsiness may be a severe complication in the treatment with Mysoline. This usually resolves after a week or ten days of continued therapy and the patients can then be continued on medication without continuing drowsiness.

Certain drugs or types of drugs are particularly efficacious in certain seizure types. The spectrum of indications is shown in Tables 1 and 2.

Major Motor Seizures

The drugs of choice in major motor seizures are the barbiturates, hydantoinates and primidones. Most neurologists do not treat a patient for a single seizure unless there are especially indicative circumstances. The young pregnant mother, the mother with an infant whom she lifts from bathinette to bed, the practicing physician, clergyman or lawyer—these are examples of the patients whom one would treat to avoid the possible stigma or physical damage that might occur with a second seizure. In these instances or after the appearance of the second seizure, one would usually begin with the use of barbiturates in moderate doses, (0.1 gram at bedtime and 30 mg. in the morning or morning and noon). If this proved ineffective and future seizures occurred, the hydantoinates (sodium diphenylhydantoin, 0.3 gram per day) would be introduced. It is important to note that the minimum effective dose of sodium diphenylhydantoin in the adult is 300 mg. per day. It is also to be emphasized to the patient that these are maintenance doses of hydantoinate and that it is usually four to five days before the medication takes effect. This amount of medication must be kept up every day. Missed dosages of sodium diphenylhydantoin must be made up. Since people repeatedly taking medications are apt to do so in an automatic way and be a little vague as to whether or not they have actually taken their medications, it is wise to have patients on sodium diphenylhydantoin (indeed on all anticonvulsants) lay out each night their daily aliquot of medications for the next day. Before retiring they can note what doses of medication they have not taken for that day and take these to maintain their daily intake of medication. If the seizures continue, the dosage of hydantoinate may be increased; if the toxic level is reached, primidone can be added to the previous nontoxic but ineffective dose of hydantoinate. The oxazolidines are not to be used for patients with major convulsions, for these drugs often precipitate this type of seizure. This was first appreciated by the early workers with Tridione when it was an experimental drug. When it was given to children who had only petit mal seizures, although it brought to a cessation the minor attacks, it precipitated major convulsions.

Petit Mal Seizures

Rarely, phenobarbital alone is efficacious in relieving petit mal seizures. Tridione or Paradione (0.3 to 2.7 grams per day) should be employed, but it is wise to utilize phenobarbital if changes in medication are made and also to prevent major seizures in patients having mixed seizures of the grand mal and petit mal types. Physicians must remember that Tridione and Paradione are potentially toxic drugs. Hydantoinates should not be used in typical petit mal seizures, for they may increase the number of seizures. Zarontin is effective in controlling petit mal seizures and may prove less toxic than the oxazolidines. If Zarontin is employed, it is customary to begin at a dose of 500 mg. per day, increasing the dosage until seizure control is reached or some sedative effect is obtained.

Focal Seizures

The medical treatment of focal seizures, be they jacksonian, major motor, temporal lobe (psychomotor) or hallucinatory seizures, is often difficult. In general, the same medications are employed as in major motor seizures. However, because of the difficulty in arriving at seizure control, one usually does not begin as gingerly with phenobarbital, but moves more rapidly into the use of Mysoline or sodium diphenylhydantoin. Indeed, many neurologists feel that Mysoline is the drug of choice in this area. Phenurone (phenacemide, acetylurea) is a potent preparation in the alleviation of psychomotor seizures, but it is so toxic and dangerous that it is not in common usage at the present time.

Other Drugs

Various preparations play a minor role in the control of seizures, but for an individual patient they may often prove of great importance. Many explorations have been made in the use of *meprobamates* in the treatment of epilepsy, and although some slight efficacy has been achieved, there is no satisfying evidence of these as outstanding anticonvulsants. Where they may play a particular role is in the rare patient whose seizures are precipitated by emotional distress and emotional problems. *Diamox (acetazolamide)* as a dehydrating agent, and indeed *Diuril* (*chlorothiazide*) may be considered in those unusual cases of seizures closely related to the menses and associated with fluid retention. However, on careful scrutiny most of the seizures attributable to the period of the menses actually bear little or no temporal relationship to this cycle in the female life. Diamox is also worth a try for the patients with petit mal epilepsy who prove recalcitrant to all other types of medication. *Elipten* (*amino-glutethimide*), a close relative of Doriden, may be of value for the patient who has not been brought under complete control with medications in more common usage. By itself it does not appear to be a strong or very potent anticonvulsant.

COMPLICATIONS OF THERAPY

Medications that are potent enough to stop seizures are potentially dangerous drugs. Phenobarbital is the safest of all anticonvulsants. Its only important complication is drowsiness. Dilantin is somewhat more toxic. Ataxia, diplopia, hypertrichosis and gum hypertrophy are considered minor complications, for they are readily controlled by decreasing the dosage or stopping the medication. Rarely there is a bullous erythematosus, and on rare occasions a psychosis has been attributed to Dilantin therapy. Mesantoin, Tridione and Paradione may cause blood dyscrasis (agranulocytic anemia) and in patients receiving these preparations it is necessary to observe blood counts at regular intervals, usually monthly. If a patient on one of these drugs develops a significant agranulocytosis, it is important to treat any minor infection vigorously with antibiotics. When the leukopenia becomes significant (a white blood cell count of 3500 per cubic millimeter or below), it is necessary to stop medication. Some of the earlier hydantoinates no longer generally available (for example, Thiantoin) and acetylurea (Phenurone phenacemide) can also cause liver damage as well as agranulocytic anemia. Acetylurea may also cause a severe psychosis, usually a depression. At the present time, this drug is very seldom employed in the treatment of epilepsy, for although it is effective in controlling psychomotor seizures, it is a dangerous preparation.

NEW PREPARATIONS

Although the recent controversy over the study of experimental drugs has somewhat damped the ardor of the pharmaceutical houses and clinical investigators, a considerable amount of work is being carried on at the present time with experimental preparations. The most promising at the moment, 7-nitro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one, is known by the code name LA-I. This drug seems particularly efficacious in the clinical experiments for the control of petit mal and focal seizures and seems to have a minimum of toxicity. An experimental preparation (Riker 594) has shown considerable promise in alleviation of seizures, but it has some peculiar untoward side effects including a hyperventilation syndrome and some emotional disturbances.[7] It is possible, though, that this preparation may again be studied. The search continues for an ideal drug, which will be nontoxic and efficacious in all types of seizures.

GOALS OF MEDICAL THERAPY

The aims and goals of medical therapy are first to bring the patient to complete freedom from seizures, then gradually to reduce the medication to the point of freedom from seizures, and finally to discharge the patient from the clinic or practice. This last step cannot often be attained, but it is certainly a worthwhile goal for physician and patient to strive toward. The patient must be induced to cooperate with the physician in arriving at the proper medication level and to take the medication regularly over a period of time. This period of time depends upon the frequency of the seizures and most particularly upon the longest free period occurring prior to the beginning of successful medication. For example, if the patient's longest period of freedom from seizures has been six months, at the end of three years of freedom one can feel quite confident that the medication has been successful and may very gradually reduce the medication over a period of several years. In the case of petit mal which is characterized by the frequency of seizures, medications can be reduced after several months of freedom from seizures. This is especially worth while when the successful medications are the potentially toxic oxazolidines.

MANAGEMENT OF STATUS EPILEPTICUS

Status epilepticus is a real medical emergency. The frequent repetition of grand mal seizures with only a few minutes intervening between seizures and without the regaining of consciousness may lead to death or neurologic deficit either permanent or transient. It is important, therefore, to stop these seizures as quickly as possible. Sodium phenobarbital intravenously is the drug of choice of most neurologists. It is administered at 20-minute to half-hour intervals in dosages of 0.2 gram or even more. Very rarely, sodium amytal is more effective than sodium phenobarbital intravenously. Paraldehyde may be used. After numerous seizures, hypertonic glucose may prove efficacious by reducing the cerebral edema which is secondary to the seizures and in turn precipitates more seizures. General anesthesia is often necessary to halt status epilepticus; one of the safest anesthetic agents is rectal Avertin (tribromethanol).

Petit mal status is not common.[9] It can be arrested by CO_2 inhalation, either by mask in a 5 per cent mixture with oxygen or by rebreathing in a bag.

SOCIAL AND PSYCHOLOGICAL FACTORS

Most patients who present themselves to the physician because of seizures are concerned about the possibilities of *mental deterioration*. They recall patients they may have known with severe brain damage causing cerebral palsy, mental deterioration and seizures. They are quite certain that this is what lies in store for them. The explanation then needs to be forthcoming from the physician that in those patients the seizures, the palsy and the retardation or deterioration all derived from the brain lesion rather than the latter two symptoms from the seizures.

The patients are also concerned about the *hereditary aspects* of epilepsy. Although it is quite likely that there is a genetic factor present, it is certainly not a dominant characteristic. It has been shown that seizures are somewhat more common in the relatives of patients with seizures because of cerebral lesions than would be expected in the total population. Seizures are much more common in patients with so-called genetic or essential epilepsy than in either the symptomatic group or the normal population. However, it is important to remember that epilepsy is not a matter of black or white, but is rather a matter of shades of gray. There is no person who could not have seizures under the appropriate stimulation, be it electrical, chemical or metabolic. Undoubtedly the epileptic has a somewhat greater potential for having offspring with seizures than is true of the control population, but the incidence is not overwhelmingly high. The possible genetic factor assumes more importance when the patient's electroencephalogram presents a generalized abnormality, when the patient has a strong positive family history of epilepsy, when the spouse also has a strong personal or family history of epilepsy, or when the spouse presents an abnormal EEG.[6]

The *epileptic personality* is largely a result of the impact of society upon the patient rather than a result of the disease per se. It is not difficult to understand how the shunned epileptic youngster, as he grows up and finds various endeavors and activities in life cut off from him, becomes self-centered, somewhat suspicious, aggressive and irritable. This becomes an important consideration in the management, particularly in working with the patient's family, schoolteachers and employers.

Modern society further complicates the problem. The invention of the gasoline engine and its adaptation to our daily way of life makes an additional discretionary factor in the handling of the epileptic. Most states have or are evolving a reasonable law allowing the epileptic to obtain a driver's license openly when he has been free from seizures two or three years, even when this freedom has been gained by the use of medication. However, licenses to operate aircraft should not be given to patients with seizures.

CONCLUSIONS

Great gains have been made in the management of the epileptic patient, but there is still room for considerable improvement. It is variously estimated that up to 75 per cent of patients can be rendered virtually seizure-free by medication. Of the remaining group, 50 to 60 per cent of those who satisfy the criteria for surgical excision of a lesion will be rendered seizure-free by operation or will be helped to the extent that their seizures are controllable by medication. This still leaves an appreciable number of patients with seizures and indeed the improvement rates on medication are probably optimistic. New therapeutic agents have been many and are appearing with ever increasing frequency. The breakthrough, however, is dependent upon determination of the actual cause of the seizures. In the latter part of the 19th century Hughlings Jackson described epilepsy as a sudden excessive disorderly discharge of the gray matter of the brain. Development of electroencephalography has not only proved this, but has proved that the discharge is electrical. Physiological and structural studies have taught us much as to the localization of lesions. It is quite apparent from histopathologic studies that the lesion is primarily not structural, but neurochemical. Relatively recent neurochemical studies point to the gamma amino butyric acid cycle and the possible role of pyridoxin. It is to be hoped that the pinpointing of the biochemical lesion will lead to the ideal medication, which will produce complete recovery from all types of seizures and without toxic effects.

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Medical and Surgical Treatment of Parkinson's Disease*

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The treatment of Parkinson's disease has been advanced considerably in recent years, in part because of the advent of satisfactory surgical procedures. Our own experiences will be dealt with at length later. Those who have come to know Parkinson's disease best recognize that (1) there is presently no cure for the disease, (2) medical and physiotherapeutic measures are still the mainstays of treatment, whether or not surgery is also used, and (3) the patient's psychologic defense against this chronic disease is a major determinant of the success of therapeutic measures and the maintenance of his place in life.

DRUG THERAPY

As in treatment of other chronic diseases, such as the convulsive disorders or diabetes, the patient should understand the rationale of the drug treatment, what drugs are being used, what therapeutic effects and what side effects may be expected. This awareness is particularly important when, as in Parkinson's disease, there are a large number of variables interacting with the illness and the drugs.

Drug therapy in Parkinson's disease depends on the anticholinergic agents, stimulants and some of the so-called tranquilizers. The anticholinergic agents especially vary in effectiveness and in the production of side effects, so they are best begun at a low dosage and then increased in amount every one to two weeks. After a trial of one drug for one or two months, it is usually worth while to try others so that eventually two or three anticholinergic agents are found which are helpful. Alternating between two helpful drugs every 6 to 12 months is usually desirable since some tolerance frequently develops.

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The most common side effects of the anticholinergic drugs are dry mouth, blurred vision due to paralysis of the muscles of accommodation, constipation, urinary hesitancy or retention (to be watched for in situations of pre-existing partial obstruction such as prostatism) and mental confusion. The last varies from a brief lapse in memory to delirium and hallucinations and is most likely to occur in those patients who already have mild organic mental deterioration.

In our experience the most useful anticholinergic drugs are the following:

1. Artane (trihexyphenidyl), Kemadrin (procyclidine hydrochloride) and Pagitane (cycrimine hydrochloride) are the best all-purpose drugs
2. Parsidol (ethopropazine hydrochloride) is frequently good for tremor, but the incidence of side effects is high.
3. Cogentin (methanesulfonate) is excellent for rigidity, but side effects are troublesome, particularly in older patients.
4. Phenoxene (chlorphenoxamine ether hydrochloride) and Disipal (orephenadrine hydrochloride) often have a mood elevating effect. The former occasionally causes diarrhea.
5. Akineton (biperiden) and hyoscine are occasionally useful.

Stimulants such as amphetamine and Ritalin (methyphenidate hydrochloride) are frequently useful in combating lethargy and fatigue. Dextroamphetamine time release capsules, in a total daily dosage of 10 to 30 mg., are usually most helpful.

Tranquilizers likely to help vary according to the patients' problems. Meprobamate or Librium (chlordiazepoxide) is good in dealing with the increased anxiety and self-consciousness produced by the disease. Often they will lead to a considerable reduction in the increased tremor and rigidity associated with public appearances. Alcohol is often good for this purpose, too. Tofranil (imipramine) has been particularly useful in treating the patient with a combination of depression and akinesia.[8]

PHYSIOTHERAPY

Physiotherapy is critical for most patients. It is particularly useful for those with rigidity or developing flexion contractures or postural disturbances. Yet, most patients, doctors and physiotherapists are unaware of the type and duration of exercises likely to help. Too often all are disappointed with the results after several weeks of massage, whirlpool baths and heat treatments. A different orientation is needed.

Physiotherapy in this chronic disease with almost constant and asymmetrical increased muscle tone should be oriented around daily active and passive exercises and postural training to be continued for the rest of the patient's life. The patient must realize not only that he is carrying out exercises for present benefits, but that the diligence and persistence he shows will retard or prevent invalidism 5 or 10 years hence. Intensive treatments for two to three weeks are often important initially, both because of the immediate gains and because of the training the patient should receive for the daily exercises at home. Similar intensive treatments every year or so are also worth while, largely because of their value as refresher courses. Exercises once or twice a week under the direct supervision of an interested and experienced physiotherapist are also of value. All these measures should be directed to supporting and guiding the therapy the patient and his family carry out at home.

Physiotherapy should revolve around stretching those muscles which tend to distort the patient's posture—usually the flexors of the trunk and neck, the adductors of the shoulder girdle, the biceps, the wrist and finger flexors, the thigh flexors and the hamstrings. Vigorous active and passive stretching of these muscles for 15 minutes once or twice a day usually suffices. The patient should learn to sit as upright as possible, using a straight chair in which the principal point of contact with the back is in the lower thoracic region. Sitting with the feet on an ottoman will allow the weight of the legs to extend the knees.

Also important are daily walking exercises, in which the patient concentrates on throwing the feet out so that the heels hit the ground first. Many other useful exercises are described by Doshay[4] and England and Schwab.[5, 6]

Another important aspect of treatment is trying to keep the patient as independent as possible in his daily activities. It is better for him to painstakingly dress himself and feed himself than to have a helpful relative do it for him.

Cultivation of an independence of mind and the maintenance of outside contacts will help to counteract invalidism and depression. Perhaps the most crippling aspects of this largely motor disease are the effects it has on the personality.

NEUROSURGICAL TREATMENT

The neurosurgical treatment of Parkinson's disease has become an important and yet controversial therapeutic measure. The controversy is many-faceted. It is still difficult for some to accept the empirical observation that surgically produced lesions, occasionally in structures previously damaged at a cellular level by the disease itself, can often alleviate tremor and rigidity.

The resulting reduction in tremor and rigidity is still equated by some to damage to the corticospinal system and/or the production of weakness. As will be shown, this is not our experience.

Wide variations in short-term results have been reported, and it is possible either to condemn or to over-rate the surgical approach depending on one's view. Some of the variations may be attributed to the selection of cases, the surgical target, the accuracy of reaching the target and the technique of making the lesion.

Variations in long-term results are also seen, but there is little documentation or explanation of these changes. This lack of data has allowed undue pessimism or optimism. Some of these problems may be clarified by the discussion which follows.

The essentials of the surgical therapy for Parkinson's disease are as follows:

Case Selection

This is of particular importance, since it has become clear that even the most technically proficient neurosurgery will fail to benefit certain types of Parkinson's disease. In our experience, the excellent candidate for surgery has good general health, is fairly youthful physiologically although not necessarily chronologically, and has symptoms consisting largely of a rhythmical tremor and some rigidity. Unilateral symptoms are more favorable since only one operation is indicated, but many people with bilateral symptoms may still be excellent candidates if one judges by the results. The excellent candidate has a normal voice and swallowing, no long motor tract signs and no mental deterioration.

The good candidate for surgery is similar to the excellent one except that the tremor is usually harsher and more irregular, the rigidity is more severe, and some akinesia may be present. Akinesia is difficult to define, but consists of slowness of movement, a difficulty in initiating movement, a loss of associated movements and a loss of quick unconscious postural adjustments beyond that which can be explained by rigidity alone. It is possible to have considerable rigidity and little akinesia or vice versa. One can detect even mild degrees of akinesia by careful inspection of the patient and make fairly accurate predictions of the degree of disability 5 or 10 years hence. Yet it is difficult to measure akinesia by objective tests.

The fair candidate for surgery has severe tremor and or rigidity, moderate incoordination on rapid, repetitive movements, moderate akinesia, some postural disturbance, dysarthria manifested by rushing words together and a trailing off of speech toward the end of a sentence, some dysphagia, some memory disturbance and some pyramidal tract signs, and needs considerable help in daily activities. The patient who is otherwise an excellent candidate but who has a passive or dependent personality, or is depressed, or is no longer actively resisting the illness should also be considered no better than a fair candidate. Too often we have seen patients with a technically excellent reduction in tremor and rigidity continue to be almost completely invalided because of such a personality state.

The poor candidate for surgery has a further exaggeration of the above symptoms and needs complete nursing care.

Skill and Experience of the Operator

The skill and past experience of the surgeon with stereotactic surgery is of considerable importance. The operation is deceptively simple, but minor missteps can result in failure to achieve reduction of symptoms and can cause a variety of undesired effects. It is also desirable, if the surgeon has the time and temperament, to postpone the operation if certain initial steps do not go satisfactorily.

Localization of Target

The localization of the target in the thalamus or basal ganglia is the single most important step in the surgical procedure. For this one needs adequate visualization of structures bounding the third ventricle such as the anterior and posterior commissures, foramen of Monro and pineal gland, and familiarity with the anatomy of the basal ganglia and thalamus and its normal and abnormal variations. Localization of the target may be materially assisted by the clinical response to electrical stimulation and also by the cortical evoked activity.[11] Other techniques such as temporary blockage of the target area by procaine instillation, by inflating the balloon on a Cooper-Bravo cannula, or by cooling but not freezing the area are also useful. The temporary cessation of tremor and rigidity as the probe tip enters the target area is also a most helpful sign.

Site of Surgical Lesion

The site of the lesion which appears to give the most effective reduction in tremor and rigidity is the thalamic nucleus ventralis lateralis. The centrum medianum, the globus pallidus and the lateral part of the substantia nigra are the other principal targets.

Technique of Making the Lesion

The technique of making the lesion is also essential to the success of the procedure. Theoretically, it is desirable to be able to make a lesion of predictable shape and size and one which can be enlarged symmetrically. It is preferable that the incremental enlargement be able to be made over minutes rather than hours or days since this permits the maximal lesion to be made in one stage and avoids the necessity of leaving a stereotactic probe in place for some time after the operation. Further, it is useful to know promptly the maximal effect to be gained at a given location since it is then possible to make another lesion nearby if necessary. On the other hand, it is preferable that the enlargement of the lesion take place over minutes rather than seconds since this permits accurate observations of the patient's neurological status and thus decreases the chances of damaging important neighboring areas. The boundary between the lesion and surrounding tissue should be as sharp as possible. The lesion should tend to coagulate blood vessels and their contents rather than erode the walls.

Comparative studies of different lesion-making techniques have not been carried out, but it now appears that a lesion made by freezing[1] most nearly fulfills the requirements. Coagulation by radio frequency waves[7] is also excellent. Radioactive yttrium[3] is limited by a relatively fixed size of lesion which is made over 24 to 72 hours, and a new operation is needed to make another lesion. Ultrasound technique[10] is cumbersome and technically difficult and appears most useful as a research tool. Monopolar and bipolar electrolytic lesions are difficult to make large enough and have other faults. The alcohol method[2, 9] in experienced hands is simple and reliable, but the lesion must be enlarged over several days. Other methods such as coagulation by heat have not been used sufficiently long to pass judgment on them.

ANALYSIS OF 149 OPERATIONS IN 114 CASES

A recent series[9] of cases treated by surgery may give some indication of the usefulness of this method. The patients were operated upon by Robert Rand or Paul Crandall. The Cooper-Bravo alcohol method[2] was the principal means of making lesions. Although it does have certain drawbacks, evaluating cases tested by this older method permitted postoperative follow-ups for one to five years.

One hundred fourteen patients were operated upon from October 1957 to October 1961. They were selected from a total of 710 seen as clinic or private patients at the University of California Center for Health Sciences, Los Angeles. The 114 patients, plus 46 who were judged to be candidates for operation but who decided against operation, plus 24 who desired operation but had it performed elsewhere, constituted 25.9 per cent of the total number. One hundred forty-five (20.4 per cent) were not considered for surgery because their disease was too recent in onset or too mild, or was adequately controlled by medicine; 381 (53.7 per cent) were rejected because the disease was judged to have progressed too far or to produce symptoms unlikely to be helped (see Case Selection).

Seventy-nine patients had unilateral operations. The youngest was 18 and the oldest 67, and the average age was 53.8. The 35 patients who had bilateral operations ranged from 38 to 69 years with an average of 54.5 at the time of the first operation. The average for the whole series was 54.0.

The duration of parkinsonian symptoms ranged from 3 to 43 years. The average was 8.8 years.

There were 56 males and 23 females in the 79 patients who had unilateral operations, and 21 males and 14 females in the 35 who had bilateral procedures. Thus, in the combined series 67 per cent were males. This compares with the 64 per cent males in the total group of 710 cases.

The etiology was unknown in 91 (79.8 per cent) of the 114 cases; 12 (10.5 per cent) had a clear history of encephalitis no more than 3 years preceding the onset of symptoms and were considered to have postencephalitic parkinsonism. We considered that another 10 (8.8 per cent) probably had postencephalitic parkinsonism on the basis of onset in youth or early middle life and the presence of one or more of the following symptoms: oculomotor palsy or oculogyric crisis, blephorospasm, dystonic posturing, a very harsh tremor and severe stuttering or rhythm disturbance in speech. One patient had parkinsonian symptoms following carbon monoxide intoxication. None of the patients was diagnosed as having arteriosclerotic parkinsonism.

Prior to surgery all patients had extensive trials of antiparkinsonian medicines and physiotherapy. Those patients who were referred directly for surgery or who were deemed to have inadequate medical management were started on a vigorous program. In a number of instances, sufficient benefit occurred so that surgery has been postponed indefinitely. Of the patients who went on to surgery, those who had carried out a daily exercise program preoperatively appeared to have a shorter convalescence and better over-all result.

One hundred forty-nine operations were performed on the 114 patients. Seventy-nine patients had unilateral operations and 35 had bilateral procedures. One hundred forty-two operations were performed using the Cooper-Bravo alcohol-Pantopaque technique[2] and 7 using a yttrium^{90} radioactive sphere on the end of the stereotactic probe.[3] In 124 instances, the lesions were made in the region of the nucleus ventralis lateralis, 9 in the region of the centrum medianum and 16 in the region of the globus pallidus.

The surgical results were evaluated on a day-to-day basis in the immediate postoperative period and at weekly and monthly intervals thereafter, with follow-ups extending from 6 months to 5 years.

The early (4 months) and late (12 to 60 months) surgical results were classified as excellent, good, fair or poor. Patients with an *excellent result* were tremor-free with the possible exception that several beats of tremor might occur with severe emotional stimuli. The rigidity was judged to be 90 to 100 per cent improved. Such patients were able to return to normal activity for their age and showed no mental or speech impairment.

The patients with a *good result* were tremor-free except for mild episodes of tremor with fatigue and emotional crises. The rigidity was improved 75 to 90 per cent. They were independent with respect to personal care and showed no increase of any previous mental or speech impairment.

The patients with a *fair result* showed persistent or recurrent mild tremor and 50 to 75 per cent improvement of the rigidity. In addition, they required some help for personal care.

The patients with a *poor result* had recurrence or persistence of rigidity and/or tremor. There might be, in addition, some increase in bulbar

Table 1. 79 Unilateral Stereotactic Operations on 79 Patients

CANDIDACY BEFORE OPERATION	No. of Patients Months post-op.		RESULTS OF OPERATION							
			Excellent Months post-op.		Good Months post-op.		Fair Months post-op.		Poor Months post-op.	
	0–4	12–60	0–4	12–60	0–4	12–60	0–4	12–60	0–4	12–60
Excellent	16	15	10 (62.5%)	11 (73.3%)	4 (25%)	3 (20%)	1 (6.2%)	—	1 (6.2%)	1 (6.6%)
Good	36	36	12 (33.3%)	10 (27.8%)	14 (38.9%)	18 (50%)	10 (27.8%)	8 (22.2%)	—	—
Fair	20	20	3 (15%)	2 (10%)	4 (20%)	8 (40%)	8 (40%)	3 (15%)	5 (25%)	7 (35%)
Poor	7	7	—	—	—	—	4 (57.1%)	3 (42.9%)	3 (42.9%)	4 (57.1%)
Total	79	78	25 (31.6%)	23 (29.5%)	22 (27.8%)	29 (37.2%)	23 (29.1%)	14 (17.8%)	9 (11.4%)	12 (15.4%)

(From Markham, C. H., and Rand, R. W.: Arch. Neurol. *8*:621–631, 1963.[9])

signs or permanent mental impairment. A poor result also included persistent hemiplegia or other major, new neurological handicap. The one patient who died following operation is classified in this category.

Patients with unilateral operations. Careful examination of Table 1 gives considerable information on the 79 patients who had unilateral operations. Several main points may be noted. Of the total group, 29.5 per cent had excellent and 37.2 per cent had good long-term results, making 66.7 per cent in whom the operation was of considerable benefit. Of the excellent candidates, 93.3 per cent had excellent or good results one to five years postoperatively. The good candidates had 77.8 per cent late excellent or good results. These figures clearly indicate the value of case selection for operation.

Patients with bilateral operations. Thirty-five patients had 70 operations, the operations on each patient being done one to twelve months apart. The results of the two operations were evaluated separately, but over-all results were judged to be equal to the poorer of the two sides. None of these patients were considered to be better than good preoperative candidates because of the bilaterality of the disease. In view of the results, it is probable that many should have been considered excellent candidates.

Of the 35 patients, two died of causes unrelated to the operation before a year had elapsed after the second operation. As may be seen in Table 2, the 33 survivors had 78.7 per cent excellent or good long-term results and 20.4 per cent fair or poor results.

Of the 21 who were good preoperative candidates, 100 per cent had excellent or good late results.

Of the 114 patients comprising this series and having a total of 79 unilateral and 70 bilateral operations, 111 survived one year. Of these late results, 38 (34.2 per cent) were excellent, 40 (36.1 per cent) were good, 19 (17.1 per cent) were fair and 14 (12.6 per cent) were poor. Thus 70.3 per cent had excellent or good results and 29.7 per cent had fair or poor results. Although these figures representing the whole group are good, it should be noted that of the 72 excellent or good candidates living one year after the operations, 63 (87.5 per cent) had excellent or good late results; this emphasizes the value of case selection.

The *complications* in these 114 patients having 149 operations are noted in Table 3. One patient in the series died (0.7 per cent). He developed acute thrombocytopenia of unknown cause in the immediate postoperative period and had a hemorrhage in the thalamus at the site of the distended balloon of the Cooper-Bravo cannula. No alcohol had been injected.

Four (2.6 per cent) patients had late mild hemiparesis. One (0.7 per cent) had severe persistent hemiplegia; in this patient a thalamic abscess developed and the hemiplegia followed the necessary surgical treatment. This was also the only intracranial surgical infection of the series.

An organic confusional state occurred immediately after 41 of the 149 operations (27.5 per cent). It was mild in 35 (23.5 per cent) and severe in 7 (4.7 per cent). There was persistent mild dementia in 2 (1.4 per cent).

Postoperative dysarthria, consisting of slurred speech, rushing words particularly at the end of a sentence, and stuttering, closely resembled that seen in Parkinson's disease in its natural state. Of 3 patients (2.0 per cent) who had early severe dysarthria, 2 had good partial improvement and one has had no definite change in two years. Dysarthria could

Table 2. Results of 70 Bilateral Stereotactic Operations in 35 Patients, Overall Result in Each Patient Being the Poorer of the Two Operations

CANDIDACY BEFORE OPERATION	No. of Patients Months post-op.		RESULTS OF OPERATION							
			Excellent Months post-op.		Good Months post-op.		Fair Months post-op.		Poor Months post-op.	
	0–4	12–60	0–4	12–60	0–4	12–60	0–4	12–60	0–4	12–60
Excellent	–	–	–	–	–	–	–	–	–	–
Good	22	21	13 (59.1%)	13 (61.9%)	8 (36.4%)	8 (38.1%)	1 (4.5%)	–	–	–
Fair	11	10	2 (18.2%)	2 (20%)	4 (36.4%)	3 (30%)	4 (36.4%)	4 (40%	1 (9%)	1 (10%)
Poor	2	2	–	–	–	–	2 (100%)	1 (50%)	–	1 (50%)
Total	35	33	15 (42.9%)	15 (45.4%)	12 (34.3%)	11 (33.3%)	7 (20%)	5 (14.3%)	1 (2.8%)	2 (6.1%)

(From Markham, C. H., and Rand, R. W.: Arch. Neurol. *8*:621–631, 1963[9].)

Table 3. Complications from 149 Stereotactic Operations

		79 UNILATERAL OPERATIONS		70 BILATERAL OPERATIONS				
	Months Post-op.	Complications		Complications After 35 First Operations		Complications After 35 Second Operations		
		Mild	Severe	Mild	Severe	Mild	Severe	
Death	0–4		1					1 (0.7%)
	12–60							
Hemiparesis	0–4	16	4	8	1	2	—	31 (20.8%)
	12–60	3	1	1	—	—	—	5 (3.4%)
Abnormal movements	0–4	6	1	8	1	5	—	21 (14.1%)
	12–60	1	—	—	—	—	—	1 (0.7%)
Incoordination	0–4	2	—	3	—	2	—	7 (4.7%)
	12–60	—	—	—	—	—	—	—
Dementia	0–4	14	3	11	1	9	3	41 (27.5%)
	12–60	2	—	—	—	—	—	2 (1.4%)
Dysarthria	0–4	4	1	3	—	2	2	12 (8.0%)
	12–60	1	—	—	—	1	1	3 (2.0%)
Dysphagia	0–4	1	—	—	—	2	1	4 (2.7%)
	12–60	—	—	—	—	1	—	1 (0.7%)
Hemihypalgesia	0–4	3	—	—	—	1	—	4 (2.7%)
	12–60	—	—	—	—	—	—	—
Seizures	0–4	1	—	1	—	1	—	3 (2.0%)
	12–60	—	—	—	—	—	—	—

(From Markham, C. H., and Rand, R. W.: Arch. Neurol. *8:* 621–631, 1963.[9])

be correlated with bilaterality of the disease, with previous speech disturbance and with a previous stereotactic operation.

Seizures followed three operations (2.0 per cent). They consisted of one or two grand mal seizures in the immediate postoperative period. Antiseizure medication was given for two or three months and was then stopped. No further seizures and no paroxysmal EEG changes have occurred in the one to two years since operation on these patients or any others in the series.

Considering the serious side effects as a group and taking into account that two or more of these complications occasionally occurred together, the chance of being worse off by dying or by having a serious neurological complication was about 1.5 per cent.

CONCLUSION

It is still too soon to place the operative treatment of Parkinson's disease in proper perspective. Five- and ten-year follow-ups are really necessary for this. However, the present study suggests that the excellent or good candidate (at least as defined by us), has a very good chance of having a significant reduction in his symptoms for one to five years. The fair or poor candidate is disabled in ways unlikely to be helped by the operation, and except in unusual circumstances, the surgical approach should be avoided.

The surgical approach to Parkinson's disease is probably an interim method until such time as more precise drug therapy can be developed. Yet it can be so strikingly helpful that, if a patient is today judged an excellent or good candidate and if proper surgical therapy is available, the author would urge proceeding with surgery.

Finally, it should be stressed again that there is presently no cure for Parkinson's disease and that the maximal alleviation of symptoms will be produced by a life-time program of physiotherapy and drugs, and by surgical therapy in perhaps 25 per cent of the cases.

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Multiple Sclerosis

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ONCE CONSIDERED relatively rare, multiple sclerosis has become better known to the general public and to physicians. Its prevalence rate in northern latitudes of about 50 cases per 100,000 of the general population suggests that even in relatively small communities of 10,000 one might expect to find as many as 5 residents of the community afflicted. The highest incidence of onset is among young adults, often just beginning to raise families, and since in many it has a long drawn out, inexorably progressive course, the medical, emotional and social problems have presented an especially appealing picture to the public and to physicians. Medical scientists have been challenged by the problem of etiology, pathogenesis and treatment of this demyelinative disorder, so that currently and for over a decade intensified research efforts have been directed toward a solution.

The disease affects primarily the central nervous system, other body tissues being uninvolved except through secondary complications. Grossly and microscopically the myelinated nerve fiber tracts of the brain and spinal cord show discrete foci of damage. The possibility that more fundamental elements, such as oligodendroglia cells, believed to form and support myelin, are the primary site of metabolic disruption, from whatever cause, has been considered. Remissions and more or less prolonged inactive periods may occur and the life span may not be materially shortened, but the majority of sufferers succumb to the disease after duration ranging from 5 to 30 years (or even shorter or longer periods). The classical pattern involves the steady accretion of motor and sensory disabilities in the lower limbs with ultimate paraplegia and confinement to a wheelchair or bed, incontinence, impairment of useful function in the upper limbs, speech and visual difficulties and, late in the disease, personality and mental deterioration. A small minority of patients, however, live out a normal life span with few or none of the disabilities just mentioned.

ETIOLOGY

Neither the etiology nor the crucial phases of pathogenesis of multiple sclerosis are known, though many hypotheses and results of investigations have been published. No longer seriously considered are such possible causes as tuberculosis, vitamin deficiency, foci of arterial vasoconstriction or venular thrombosis due to primary blood or blood vessel factors, exogenous allergic factors, exogenous intoxication from or deficiency of trace elements in the soil (lead and copper, respectively), and other more remote suggested causes.

Possible predisposing, precipitating or aggravating factors, potentiating, initiating or enhancing whatever the basic pathogenesis might be, have received much attention but controlled scientific investigation provides satisfactory support for the roles of only a few. Among these, it seems likely that hereditary and familial factors play a part in predisposing the individual to the development of disease inasmuch as over 6 per cent of sufferers have relatives with multiple sclerosis, and the existence of several cases in the same family is not uncommon.[5, 26, 30, 39] In an allegedly higher proportion of attacks (first or recurrent) than would be expected by chance there appears to be preceding infection, especially respiratory.[29] Many other stressful factors, however, have also been claimed to bring on episodes, such as emotional upsets, physical exhaustion, operations, anesthesia, physical injury and pregnancy. Special studies have been made of the possible relationship of some of these factors, notably physical injury and pregnancy, to the precipitation of or worsening of the disease, and the conclusion has been reached that concurrences were likely coincidental or nonspecific.[7, 19, 31, 44, 50] Since the disease progresses irregularly and unpredictably, with great variation in intensity and duration of relapses, the most rigorous scientific control must be exercised and statistical principles must be soundly applied in the analysis of the possible influence of such factors.

The contribution of a specific dietary factor, namely, high fat intake, to the pathogenesis of lesions has been emphasized in one study.[48, 49] The results suggested that rigid maintenance of a low fat intake (less than 15 grams per day) prevented relapses and steady downhill progression in the disorder. The hypothesis of lesion production was centered on postprandial lipemia, which was alleged to impair the suspension stability of erythrocytes with consequent intravascular sludging and the formation of perivascular nervous lesions. Experimental work in animals supporting this hypothesis and the clinical results of treatment have not been confirmed by other investigators.

The possibility that multiple sclerosis is an infectious disease has not yet been abandoned. Over the years studies attempting to isolate organisms from human tissues, to transmit the disease to animals, to demonstrate significant antibody titers, etc., either have been unsuccessful or have led to equivocal results or conclusions that could not be verified by others.[16] Interest in a spirochetal organism as a possible causal agent was renewed in 1957 with the unconfirmed report of cultivation of spirochetes from the spinal fluids of multiple sclerosis patients. After extensive further work by other investigators, it now seems certain that the originally reported findings were artifacts and that the organisms reported were not in any way related to the cause of multiple sclerosis.[23]

Among possible infectious causes, virus infection continues to be suspected but remains unproved after a large number of investigations with both negative and allegedly positive results.[18] Demyelinating diseases due to identifiable viruses occur in nature, both in animals and in man. In the past decade specific agents such as the viruses of herpes simplex,[40] rabies,[51] and, most recently, measles[1] have been suggested as possible etiologic agents on the basis of indirect evidence. To date these possibilities remain unconfirmed and, in the case of measles, negated.[38a] Virus infection has been thought capable of initiating an immunologic response as the more direct cause of lesions,[34] but if multiple sclerosis is a hyperimmune disease, the initiating factor is not yet clear.

The theory that multiple sclerosis is fundamentally an antoimmune disease is at present the one most widely held[34, 25] and has support in a large body of evidence, including data from clinical, pathologic, immunologic and chemical studies. The production of experimental "allergic" encephalomyelitis in animals in 1933 (induced by the injection of brain tissue) was one of the early discoveries leading to the investigation of hypersensitivity factors in the pathogenesis of the lesions of multiple sclerosis.[56]

Clinically, features of exacerbation and remission are consistent with a fluctuating hyperimmune process. Acute phases are little different from attacks of postinfectious encephalomyelitis which are thought on good grounds to represent an isoallergic reaction of the central nervous system to liberated products of CNS damage.[13, 35] On morphologic grounds, the microscopic appearance of multiple sclerosis lesions has features which have been interpreted as most likely allergic in origin.[2, 12] Alleged indications of a constitutional disorder of the delayed type of hypersensitivity were derived from the marked distortion of spinal fluid inflammatory response to intrathecal tuberculin injections among tuberculin-positive multiple sclerosis patients as compared to non-multiple sclerosis tuberculin-positive controls.[46]

Chemical evidence of possible immunologic significance is the finding of disproportionate elevation of the gamma globulin content of the cerebrospinal fluid in relation to the total protein content in a high proportion of cases of multiple sclerosis in the absence of a raised concentration of this type of protein molecule in the serum.[58] Since gamma globulins are the major protein fractions functioning as antibodies, and since neither serum nor spinal fluid has as yet been shown to contain significant identifiable anti-infectious antibodies, the elevation of this protein fraction in the spinal fluid has been interpreted as originating in the nervous tissue primarily owing to hyperimmune reactions.[25] In experimental allergic encephalomyelitis the suppression of the characteristic rise in CSF gamma globulin and of the inflammatory disease by the administration of corticotropin or corticosteroid provides further presumptive evidence linking hyperergic tissue response to the causation of multiple sclerosis lesions since studies have also shown depression of CSF gamma globulin in multiple sclerosis following administration of prednisone.[59] Finally and most recently, evidence bearing on this point is derived from the effect on myelin tissue cultures of serum from animals affected with experimental allergic encephalomyelitis and from human subjects with multiple sclerosis and other demyelinating disorders. In control studies, demyelination of these cultures was routinely produced in all cases when the cultures were exposed to serum from rabbits with experimental allergic encephalomyelitis and when exposed to the sera from over half the cases of demyelinative conditions, including multiple sclerosis.[9] This process could be reversed on removing the added noxious substances from the sera by washing the culture with saline. Nevertheless, though there appear to be circulating antibodies to brain tissue in demyelinative conditions, including multiple sclerosis, it has not been proved that they specifically produce any of these diseases.

Basic studies of the structure, chemistry and metabolism of central nervous system tissue, with specific reference to the myelin sheath and related cellular elements, have been in progress and continue presently in increasing numbers. The fine structure of the laminated myelin sheath and its probable origin in concentrically wrapped oligodendroglial cell processes has been elucidated by recent work with the electron microscope.[14] The fixed chemical structure of myelin and its molecular pattern have become more intimately known through x-ray diffraction and polarized light studies, more accurate quantitative analytical techniques for the determination of protein and lipid compounds in the white matter, and the development of the techniques of microchemistry. Histochemical studies of enzymes, the use of radioactive labeled precursors involved in lipid synthesis in the central nervous system, and microchemical techniques have shed light on the possible origin, metabolic maintenance, normal catabolic sequences, and mode of pathologic breakdown of myelin.[21, 22] For over a quarter of a century, demyelination as a morbid process has been studied in the experimental laboratory, and many different techniques for inducing it have been demonstrated. From these studies it has become obvious that demyelination is probably a nonspecific early degenerative change of white matter short of actual necrosis and, as such, does not have sufficient specificity to warrant the conclusion that there is but a single factor involved in the various "demyelinating" diseases of the nervous system.[17, 55]

Whether myelin is a relatively inert substance once laid down or a slowly metabolizing one with a specific turnover of components remains an intriguing question,[57] inasmuch as the existence of the latter condition would bring more directly into focus the fundamental role of the glia (most likely oligodendroglial cells, whose processes are now believed to make up the layered myelin sheaths of the nerve fibers) in the genesis of myelin breakdown. One theory holds that multiple sclerosis is essentially a disease of oligodendroglia which are possible sites of cellular damage from antigen-antibody combination or of damage from other noxious factors.[30]

The peculiar and as yet unexplained geographic distribution of multiple sclerosis likely has some bearing on the cause of the disease. Extensive epidemiologic investigations have now shown a comparatively low incidence in the more southern latitudes of this country and a progressive rise in incidence and prevalence in the northern areas of United States and Canada.[6] A similar higher incidence appears to exist in the colder climates of Europe. Clues to the etiology of multiple sclerosis have been sought in this relationship but as yet no pathogenetic factors clearly related to this geographic distribution have been uncovered.

TREATMENT

For decades treatment programs have been recommended and sometimes widely adopted because of alleged therapeutic benefits, only eventually to fall into disrepute. No therapeutic measure directed at the fundamental disease process can be said to have been truly successful to date. The current vogue of administering corticotropin or adrenal corticosteroids for acute phases of the disease requires additional scientifically controlled studies to confirm present optimistic appraisal of their beneficial effects. Until recently, few rigorously controlled experimental trials of therapy were carried out. The difficulties of judging the effects of therapy have often been emphasized.[27, 38, 41, 42, 43, 45] These are: (1) uncertainties in diagnosis in a proportion of presumed cases; (2) unpredictability of the course of the disease, with spontaneous remissions; (3) the existence of only crude parameters for estimating improvement or worsening of the basic disease process; (4) the irreversibility of old gliotic lesions (scars) and their masking effect on the course of fresh lesions; (5) psychological disturbances hampering the objectivity of patients' subjective reports; (6) difficulties of keeping groups of patients undergoing experimental trials of therapy under standard conditions of control; (7) unwillingness or inability of investigators to adopt a rigorous experimental methodology in evaluation of treatment.

Though no curative or finally proved ameliorative treatment directed at the disease process itself has become available, some of the therapies reported will be mentioned.

The management of multiple sclerosis is best considered under three categories of treatment whose goals are, respectively, (1) the hoped-for direct effect on the specific disease process itself, (2) the amelioration of symptoms per se, and (3) the prevention or counteraction of secondary complications.

Treatment Directed Presumptively at the Lesions Themselves

Because of the confusing array of reports in the literature over the past decade, it seems wise here to state that none of the following methods of treatment, all favorably reported, has been substantiated as effective and none is any longer in wide use or strongly advocated: vasodilators such as parenteral histamine, tetraethyl ammonium chloride, and other agents; sustained anticoagulant therapy for the prevention of relapses or further progression; anti-allergy measures such as desensitization injections and food elimination diets; the chemotherapeutic agent isoniazid; injection of an allegedly specific viral vaccine developed in Russia; and the administration of the oral hypoglycemic agent tolbutamide.

A rigorously restricted low-fat diet has been reported to result in a reduction in the frequency of relapses and in maintained improvement of neuromuscular disability in a group of patients followed for over 10 years.[48, 49] The application of statistical principles and the use of patients as their own controls before and after treatment is utilized to support these conclusions, but the value of this approach has not been confirmed by other investigators.

The place of corticotropin and orally administered adrenal cortical hormones in the treatment of multiple sclerosis remains unsettled. At present they are believed to exert an ameliorating effect, shortening the period of illness during acute exacerbations. The earlier reports were impressionistic and based on claims of more rapid defervescence of acute episodes than might occur spontaneously. Recent experimental trials of therapy utilizing these substances have been somewhat better controlled.

Attempts to quantitate data in the therapy of multiple sclerosis with ACTH are described in several papers and a monograph by one group of investigators.[3, 4] In the opinion of these authors, ACTH may be profitably given on a maintenance basis over prolonged periods to patients exhibiting a rapid downhill course. Variable dosage regimens are described in the monograph, to which the interested reader is referred.

In a study utilizing a randomly chosen matched control group,[33] ACTH was administered for fresh attacks of neurologic dysfunction in which no sign of spontaneous regression had as yet appeared up to 14 days. The dosage plan consisted of the intramuscular injection of ACTH gel in amounts of 60 units twice daily for one week, reduced to 40 units twice daily for one week, followed by injections on alternate days of 60, 40 and 20 units in succession during the third and last week of therapy. Comparison with matched controls strongly suggested a significant difference in favor of the ACTH-treated patients.

Intravenous therapy was considered preferable for the acute episodes of multiple sclerosis in another study,[53] in which the dosage plan consisted of 20 to 40 units of ACTH given daily in slow intravenous infusions for two to four weeks, followed by the intramuscular injection of 20 units of ACTH gel two to three times per week, tapering off to none over a variable period. The favorably reported results suffer from lack of satisfactory scientific controls.

Personal communication[20] and personal experience have revealed instances of rapid recovery from severe widespread neurologic dysfunction in acute episodes of multiple sclerosis associated with the administration of massive oral doses of prednisone (200 mg. daily during the first week and 100 mg. daily for the second week) followed by progressive reduction in dosage at the rate of 10 mg. daily for one week and to none by the end of the fourth week. All necessary precautions to protect against potentially serious side effects were taken. Several injections of intramuscular ACTH were given after the course of prednisone therapy if evidence of adrenal cortical hypofunction arose. It is not known, however, whether the dramatic changes in some of these patients were coincidental and related to other factors (e.g., hospitalization, rest, diminished anxiety, use of sedatives and ataraxics, etc.) or represented specific responses to steroid therapy.

Many difficulties lie in the path of deriving valid conclusions from an experimental trial of therapy. Among these is judging the course of the disease—more specifically, quantitatively measuring improvement or worsening. At the Symposium on the Evaluation of Drug Therapy in Neurologic and Sensory Diseases held at the University of Wisconsin in May 1960 under the auspices of the National Institute of Neurological Diseases and Blindness,[15] one panel studied the problems inherent in treating multiple sclerosis. As an outgrowth of these discussions an Ad Hoc Committee on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis was formed to explore further the complex problems to which it was believed insufficient attention had been given in previous reports of therapy. The published report of this group[45] emphasizes principles and suggests guide lines which hopefully will lead to sounder evaluation of trials of therapy in multiple sclerosis in the future.

Symptomatic Treatment

Until the benefits of any type of allegedly specific therapy can be more widely substantiated, symptomatic therapy will remain the most important aspect of the management of patients with multiple sclerosis. Such therapy is directed toward the amelioration of motor dysfunction, the alleviation of bladder and rectal dysfunction, minor help for visual disturbances, the improvement of pernicious emotional reactions and mood disorders, and the reduction of pain.

MOTOR DYSFUNCTION. Weakness, muscle wasting, ataxia, intention tremor, impairment of fine skilled acts, spasticity, involuntary reflex spasms, and muscle contractures restricting full range of joint motion are disturbances which may be counteracted by physical therapy in some cases. The usefulness of physical therapy may be overemphasized in this disease, for it should be remembered that it has no value for non-motor symptoms (visual, speech, sensory, bladder, etc.) and is probably contraindicated in acute phases of the disease in which rest would appear to favor reparative processes in the central nervous system. In those cases in which slow, steady downhill progression is evident, it may help to slow the rate of motor incapacitation.

The maximal usefulness of physical therapy appears to be for those patients who have residual motor disabilities but are in a relatively static phase of the disease. Here, active resistance exercises to improve power of limb and trunk muscles, daily passive stretching to counteract spasticity in order to delay inevitable contracture, and coordination exercises are helpful. Gait training, to improve efficiency and safety, and aid in learning new ways of achieving the innumerable daily acts of living are of special importance in increasing the independence of such patients.

The application of external cold, either generally or locally, has been advocated to relieve symptoms.[54] This has been done through cold baths, ice packs to limbs and even to the head, neck and spine with the goal of cooling the brain and spinal cord. Reduction in spasticity, increase in strength and other benefits are alleged to result from this modality, but these improvements disappear with warming. The mechanism for such improvement is unknown.

Drugs to relieve spasticity and reflex spasms continue to be evaluated but as yet no ideal agent for this purpose is available. Mephenesin (Tolserol) and curare are but little used for this purpose now. Chlorpromazine (Thorazine) and meprobamate (Equanil, Miltown), zoxazolamine (Flexin), methocarbamol (Robaxin), chlorzoxazone (Paraflex), and carisoprodol (Soma, Rela) may have slight muscle relaxing properties on oral administration but appear to be more useful for muscle spasm secondary to pain than for spasticity due to pyramidal tract disease.

When spasticity is extremely severe, with hyperadduction or excessive involuntary flexion spasms of the lower limbs, especially when deformity due to contractures is inevitable, the likelihood of regaining useful function of the lower limbs is remote. In such instances, surgical intervention may be carried out as a measure of last resort for symptomatic help. This may be selective alcohol block or surgical section of the sciatic or obturator nerves or the lumbosacral nerve roots intraspinally to bring about permanent relaxation of lower limb muscles. Such procedures usually add greatly to the patient's comfort and alleviate nursing problems, though permanent paralysis of the denervated muscle groups must be accepted.

The effect of thalamotomy in diminishing intention tremor[11] has not been studied in a sufficient number of cases to provide knowledge of its value. Surgical injury to the brain should be undertaken with some caution in this disorder, especially in view of evidence in animal experiments that physical trauma to cerebral white matter can reactivate a localized demyelinating process.[8] In two patients personally observed, the benefit derived from the operation in cases of advance disease underlying severe intention tremor was disappointing.

Bladder and Rectal Dysfunction. The lesser degrees of bladder dysfunction such as urgency, frequency and occasional mild incontinence may be effectively relieved through the use of anticholinergic drugs including the belladonna alkaloids, especially atropine, and the synthetic preparations such as propantheline (Pro-Banthine) and isopropamide (Darbid). Though fecal incontinence is less common than urinary incontinence, these drugs similarly inhibit involuntary rectal overactivity. The more common rectal symptom of constipation has been effectively treated by use of an oral detergent, dioctyl sodium sulfosuccinate (Doxinate, Colace), and mild peristaltic stimulants such as senna derivatives (Senokot) or cascara. Another preparation sold commercially for the latter purpose is 1,8-dihydroxyanthroquinone (Dorbane). Many patients are able to establish fairly regular bowel habits with spontaneous evacuations every second or third day through the help of these agents. For other patients regular bowel emptying is impossible save with the use of regular given enemas, usually not more often than at two- or three-day intervals.

For patients with more advanced disease who have total loss of bladder control, an indwelling catheter is essential to counteract the damaging effects of chronic urinary retention. The catheter may be attached to a tidal drainage apparatus, providing rhythmic and somewhat more physiologic filling and emptying of the bladder, or simply to a dependent rubber draining tube leading to a reservoir. Rubber urinals strapped to the thigh or leg are useful and practical for this purpose if the patient is ambulatory or in a wheel chair.

Visual Disturbances. The blindness or near blindness of acute retrobulbar neuropathy has a good prognosis for spontaneous recovery in two to eight weeks. As implied previously, recovery may possibly be hastened by the administration of ACTH or adrenal cortical hormone. Residual impairment of visual acuity following retrobulbar neuropathy, however, cannot be symptomatically helped and patients should be discouraged from seeking repeated refractions and changes of lenses. Diplopia, present as long as both eyes are open, may be eliminated by using a plastic eye shield alternately covering one eye or the other.

Mood and Emotional Disorders. Some patients with multiple sclerosis are euphoric and apparently in little emotional distress. Others, however, are irritable, dissatisfied, tense, apprehensive or depressed. Psychotherapy may be used to excellent advantage for such patients.[24]

The long-term use of the newer ataraxics or antidepressants is justified if an ameliorating effect on the emotional disturbance can be demonstrated by trial of one of these agents. Drugs of the phenothiazine group such as chloropromazine (Thorazine) or of the monoamine oxidase inhibitor group such as nialamide (Niamid) may lead to sustained improvement when anxiety or depression, respectively, are prominent.

PAIN. Pain is an infrequent symptom of multiple sclerosis occurring rarely in the face and resembling trigeminal neuralgia. High doses of orally administered nicotinic acid (400 to 800 mg. a day) may be associated with the relief of the paroxysms, but this as well as the response to parenteral vitamin B_{12} has been very inconsistent. Sodium diphenylhydantoinate (Dilantin) in the usual dosage (0.3 to 0.4 gram daily), shown to be of value in tic douloureux, may be effective in paroxysmal facial pain in multiple sclerosis. Peripheral alcohol block of the involved trigeminal division as a temporary measure followed by eventual trigeminal root section has been resorted to for persistent and recurrent pain.

Treatment of Secondary Complications

URINARY TRACT. The complications of bladder dysfunction are secondary infection, formation of bladder calculi and obstruction of bladder drainage from encrustation of the catheter. Prevention of these complications is aided by daily irrigation of the bladder with 180 to 240 cc. of 0.5 per cent acetic acid, liberal intake of liquids, substitution of clean sterile catheters at intervals, and administration of antacid colloidal aluminum gel, claimed to inhibit the urinary excretion of phosphates. If there is no encrustation of the catheter and no evidence of acute infection, the catheter may be left in place indefinitely. Regular urinalysis to determine the degree of invetable pyuria and culture of the urine when there is systemic or local evidence of an acute flare-up of genitourinary tract infection should be carried out, followed by treatment with appropriate chemotherapeutic and antibiotic agents when indicated. These should never be given over a long period or used prophylactically.

DECUBITI. When patients are chair-ridden or bedridden, decubitus ulcers sooner or later become a problem and should be treated by the usual conservative measures, which will often lead to healing: avoidance of further pressure; application of wet dressings; antibiotic solutions or ointments; and after clearing of local infection, simply exposure to air or heat lamp followed by dry sterile dressings. Unless the patient is virtually moribund, surgical repair may be carried out, including debridement and grafting.

PULMONARY AND TERMINAL. The complication of acute pulmonary infection is treated in the usual way. In patients with far-advanced multiple sclerosis, aspiration pneumonia or hypostatic pneumonia may be a terminal event regardless of therapy.

PROGNOSIS

The duration and course of multiple sclerosis are extremely variable. In rare instances, the disease may run a very short course leading to death within a few weeks. Such fatal first attacks cannot be reliably differentiated clinically from acute or subacute disseminated encephalomyelitis in the absence of common infectious antecedents of the latter. At the other extreme, the disease may last indefinitely without shortening the life span at all, characterized by reversible attacks of symptoms at widely separated intervals years apart. Cases are on record in which the disease has existed for 40 to 60 years, death supervening from other causes. Either no disability or but slight to moderate disablement may develop in such patients, even after years of multiple sclerosis, subsequently proved by the finding of minimal lesions at autopsy. Though uncommon, such a favorable course has been referred to as "benign" multiple sclerosis.[28]

The majority of patients with onset in young adulthood (between 20 and 40 years of age) pursue the characteristic course, so familiar to physicians, of exacerbations and remissions during the first five to ten years, by which time the steady accretion of residual symptoms and signs, following progressively less recovery from successive attacks, usually leads to moderate or severe disability. From this time forward the course, though fluctuating with recognizable periods of worsening and static phases if closely observed, is one of slowly progressive decline in motor and sensory functions of the limbs and trunk, excretory functions, head functions (visual, ocular, speech, swallowing), and in some instances, personality and mental deterioration. When the latter is slight or absent, patients often retain surprising capabilities and drive for accomplishment despite severe incapacitation otherwise. Patients may be confined to a wheel chair after 10 to 15 years but live on for an additional 10 or 15 years. Patients may live for 5 to 10 years after becoming bedridden. Much depends on the environment, the availability of devoted family members, and the excellence of medical and nursing care.

The opinion has been expressed that the major activity of the disease runs its course during the first five years, after which exacerbations diminish or cease, subsequent progression being due to parenchymal damage from slowly progressive scar formation (gliosis).[3] Though this may be the pattern in some patients, it is more likely that the pathogenetic factors involved and the innate resistance to the disease vary widely in intensity from one individual to the next, and on both clinical and pathological grounds there is much to suggest wide differences, quantatively and temporally, in lesion formation. Much of the apparent reduction in relapse rate in the later years of the disease may be due simply to masking of the effect of fresh lesions by already present damage and tract degeneration below the level of new lesions.

The course and outcome in any given individual cannot be accurately predicted. Prognostic factors have been analyzed in several monographs.[3, 30, 36] Certain features permit rough estimates of the future course based purely on probability factors derived from analysis of previous groups of cases.[10] The figure for the average duration of the disease would seem to have little predictive value for the individual because there is such a wide range of durations. The figure has been computed statistically in various ways and has been given as low as nine and as high as 27 years. It has been shown that late onset (after age 40) is more apt to be followed by a steadily progressive downhill course and a relatively short life span, averaging ten years.[37] Early onset (under 23) has a greater likelihood of being followed by an early remittent course, and a later prolonged, slowly progressive course with no shortening of the life span. Motor disabilities, especially incoordination and intention tremor, have a poorer outlook for recovery than do sensory, visual and ocular symptoms. Numbness and tingling, amblyopia and double vision tend to remit early in the disease, though they may become permanent later in severe, progressive cases.[30]

One retrospective analysis of the course of the disease in a group of patients showed that 13 per cent still had no major disability after 15 years, 38 per cent after ten years, and 60 per cent were without disability five years after onset.[29]

SUMMARY

To the public and to physicians multiple sclerosis has become a familar neurological disorder with rather characteristic symptoms, signs, disability and course. For many years well-intentioned efforts to treat the disease have failed because of lack of knowledge of etiology and pathogenesis. Unfortunately, many reports of therapy were initially favorable because of unsatisfactory scientific control, leading to waves of therapeutic optimism followed by disappointment. Great emphasis at present is being placed on fundamental investigations of the normal and pathologic structure, chemistry, metabolism and function of myelin and related cellular elements in the central nervous system, with the expectation that this knowledge will finally clarify etiology and pathogenesis, opening the way to rational and effective treatment. In the meantime, attention is being given to the scientific principles which must be applied in the sound evaluation of specific treatment measures. Fortunately, general supportive measures, symptomatic treatment and treatment counteracting complications have advanced to the point of materially increasing the comfort and prolonging the life span of patients afflicted.

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Multiple Sclerosis and Cerebrospinal Fluid

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THE CEREBROSPINAL FLUID is unique among body fluids. This fluid not only surrounds the brain, fills its ventricular cavities, penetrates it by way of the Virchow-Robin spaces, but also is in close contact with its blood supply as well as the blood and lymphatic supply of its covering membranes. There is some evidence to support the hypothesis that cerebrospinal fluid is a pool of extracellular fluid very similar to that in the glial cells. It is possible that the concentration of constituents which are in the glial cells is regulated by the same mechanisms that regulate the composition of cerebrospinal fluid.[24] Therefore, by studying this easily obtained body fluid, the health and/or disease of the nervous tissue to some extent can be determined.

This review of cerebrospinal fluid will deal with a discussion of the current formulation of the multiple sclerosis cerebrospinal fluid syndrome, as well as certain recent studies on its constituents which appear to be most significantly altered in multiple sclerosis.

THE MULTIPLE SCLEROSIS CEREBROSPINAL FLUID SYNDROME

An elevated percentage of gamma$_2$ globulin in the cerebrospinal fluid immunochemically* determined in the presence of a negative serological

* In our Clinic the average percentage of gamma$_2$ globulin is 12.9 ± 2.1; the standard deviation range (average ±2 standard deviations) is 8.7 to 17.1. However, the frequency distribution graph in our group of normal university students (18 to 35 years) was skewed to the right, so the range has been expressed in percentiles: 10th to 90th percentile is 10.2 to 15.8 per cent and 5th to 95th percentile is 8.2 to 16.1 per cent.

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test for syphilis in a patient who has not had syphilis, a total protein concentration less than 100 mg. per 100 ml., a normal serum gamma_2 globulin concentration, and a leukocyte count of <50 cells per cu. mm. composed of <0.5 per cent polymorphonuclear cells and mostly mononuclear cells (small > large lymphocytes and monocytes) are due to multiple sclerosis until proved otherwise in our experience in the University of Michigan Multiple Sclerosis Clinic. In spite of this experience, our most recent data indicate that only 50 per cent of 387 patients with the diagnosis of definite clinical multiple sclerosis have this cerebrospinal fluid syndrome. This incidence is lower than the most extensive report in the literature; Yahr, Goldensohn, and Kabat reported 66.5 per cent.[26]

In those laboratories which do not determine gamma_2 globulin immunochemically, the colloidal gold curve or gum mastic curve is of some value. In the same series of patients used to determine the incidence of an elevated percentage of gamma_2 globulin reported above from our Clinic, the colloidal gold curve (first zone) or gum mastic curve was found abnormal in approximately 25 per cent.

It is of some importance to mention here that Kabat, Hander, Moore and Landow in 1943[8] found that gamma_2 globulin was important in the colloidal test but albumin inhibited this reaction. Others have confirmed this observation and added that increase in alpha globulins will stabilize the colloidal gold and cover up gamma globulin increases.[2] Hence it may not be unexpected that a direct determination of gamma_2 globulin in multiple sclerosis spinal fluid should give a higher incidence of abnormality when compared to the nonspecific colloidal test results.

In many medical centers the colloidal tests (gold and especially the gum mastic) have been discontinued because of the instability of the colloidal reagent, which produced erratic results. The colloidal tests have been replaced by certain qualitative globulin tests, especially the zinc sulfate turbidity test.[5] In our own series of 387 patients with the diagnosis of definite clinical multiple sclerosis, approximately 75 per cent had a 1 or more plus turbidity in contrast to an incidence of approximately 1 per cent for 138 normal university students.

Further comments on the zinc sulfate technique for estimation of spinal fluid protein are appropriate here. Roboz et al.[12] reported that zinc sulfate under certain conditions precipitated quantitatively and selectively globulins of the mobility of gamma_2 globulin. On the other hand, Dr. Robert F. Johnston and I (unpublished data, 1956) studied the Roboz et al. method. We found that 20 per cent of Armour's crystallized bovine plasma albumin solution regularly was precipitated under conditions recommended by them and under many different conditions, such as changes in ionic strength and pH of buffer, as well as Zn^{++} concentration at different incubation times. Curiously, dilution of spinal fluids produced a more efficient precipitation of added purified gamma_2 globulin obtained from Michigan State Laboratory and Squibb Co.

Finally the best quantitative recovery of gamma$_2$ globulin was approximately 60 per cent.

Moreover, Hass and Hochwald[7] recently utilized the technique of immunoelectrophoresis on precipitates of proteins from cerebrospinal fluid prepared by the Roboz et al. method. They found a mixture of proteins (albumin > alpha globulins) and not solely gamma$_2$ globulin. They concluded that this method of cerebrospinal fluid estimation should be described as a zinc precipitin technique and not as a gamma globulin determination.

With these critical studies in mind, it should come as no surprise to find only partial correlation between the zinc precipitin protein technique and other methods which specifically estimate the concentration of gamma$_2$ globulin in cerebrospinal fluid. For example, in our own series 75 per cent of 387 patients with the diagnosis of definite clinical multiple sclerosis had an abnormal zinc sulfate turbidity test, in comparison to only 50 per cent when the immunochemical procedure for gamma$_2$ globulin was used.

Table 1. Percentage of Patients with Diagnosis of Definite Clinical Multiple Sclerosis in Remission or in Relapse with Increased or Decreased Cerebrospinal Components (Lipids, Total Protein, Gamma$_2$ Globulin and White Cells)

CEREBROSPINAL FLUID COMPONENTS (Mean ± Standard Deviation)	REMISSION (40 Patients)		RELAPSE (41 Patients)	
	% Increase*	% Decrease†	% Increase	% Decrease
Neutral fat (0.417 ± 0.242 mg./100 ml.)	6	0	10	0
Total cholesterol (0.395 ± 0.88 mg./100 ml.)	6	4	12	12
Per cent free cholesterol (33 ± 8)	10	0	12	0
Lecithins (0.228 ± 0.055 μM./100 ml.)	14	11	20	18
Total protein (38.2 ± 10.4 mg./100 ml.)	15	0	19	0
Observed total lipids (1.252 mg. ± 0.243 mg./100 ml.)	16	5	24	11
Sphingomyelin phosphorus (0.119 ± 0.029 μM./100 ml.)	17	0	18	0
Cephalins (0.152 ± 0.040 μM./100 ml.)	17	2	19	3
Observed total phospholipids (0.521 ± 0.090 μM./100 ml.)	20	7	19	14
Free cholesterol (0.122 ± 0.033 mg./100 ml.)	23	0	20	0
White cell count (1.8 ± 1.2/cu. mm.)	29	0	60	0
Nonphosphorus sphingolipids (cerebrosides) (0.094 ± 0.056 μM./100 ml.)	39	0	37	0
Total sphingolipids (0.214 ± 0.060 μM./100 ml.)	40	0	51	0
Per cent gamma$_2$ globulins (12.9 ± 2.1 %)	46	0	52	0

* % Incr.: Percentage of patients who had values > average plus 2 standard deviations; expected value is 2.5%.

† % Decr.: Percentage of patients who had values < average minus 2 standard deviations; expected value is 2.5%.

A worsening of the clinical picture in multiple sclerosis is occasionally reflected by further abnormal findings; just after an acute exacerbation the spinal fluid white cell count may become elevated or further elevated. In a study of 81 patients given the diagnosis of definite clinical multiple sclerosis in our Clinic, approximately 29 per cent of 40 patients had an abnormal white cell count (> 4.7 white cells per cu. mm.) when in remission for over one month and less than one year. On the other hand, 60 per cent of 41 patients in this study had an elevated white cell count when in relapse for over two weeks and less than two months. Other spinal fluid components studied in our laboratory showed less striking changes when the patient had a relapse (see Table 1).

SPECIAL INVESTIGATIONS

This section of the review will be limited to immunoglobulins, white cells, and lipids in the cerebrospinal fluid as well as movement of bromide ion from the blood into the cerebrospinal fluid. Those who would like to know the status of electrolytes, certain enzymes, neuraminic acid and other aspects of proteins in multiple sclerosis—especially immunoelectrophoretic aspects—are referred to the excellent recent articles by Plum and Fog,[11] Schumacher,[13] Plum,[10] Bauer,[2] and Dencker and Swahn.[4]

Immunoglobulins

The careful work of Yahr and his associates[26] and of many others, utilizing very different methods,[2] leaves little doubt that the elevation of gamma_2 globulin in the spinal fluid of patients with multiple sclerosis is a common finding and with certain limitations it may be a unique one. Therefore, from the clinical point of view, it seems most urgent to make a great effort to determine the significance of this increase in patients with multiple sclerosis. It may be that it is related to the etiological agent producing multiple sclerosis.

In pursuit of the determination of the significance of the elevation of the gamma_2 globulin in the spinal fluid of patients with multiple sclerosis, the following hypothesis has been proposed: Could an elevation of a specific antibody be the reason for an increase of the gamma_2 globulin in the fluid of patients with multiple sclerosis?

Based on the work of Sober and Peterson,[14] it appeared possible to test this hypothesis at least in part, in spite of the fact that the multiple sclerosis antigen is unknown (or nonexistent). Sober and Peterson applied ion exchange cellulose chromatography to pooled hyperimmune gamma globulin serum and showed that certain antibodies could be separated. Their data on serum indicated that group separation of antibodies was possible with this physicochemical method.

Tourtellotte et al.[22] standardized an ion exchange cellulose chromatography method and applied it to spinal fluid from normal persons, patients with multiple sclerosis and patients with neurosyphilis. Gamma globulins were isolated by passing spinal fluid through di-ethyl-amino-ethyl-cellulose exchangers. The isolated gamma globulins were then rechromatogrammed on carboxy-methyl-cellulose. Two distinct peaks from multiple sclerosis and syphilitic fluids but not from normal fluid were isolated; these are shown on the extreme right hand side of Figure 1.

Immunoelectrophoretic studies[4] of spinal fluid gamma globulins showed the precipitated gamma_2 globulin to present as an extended arc. This extended shape of the precipitate has been explained by the existence of electrophoretically different proteins that are nevertheless immunologically identical with the ordinary antisera. It is possible in our study utilizing another physicochemical method, namely chromatography, that we have fractionated this extended arc.

It has been suggested that the second peak, which we have named CM-II, is a gamma_2 globulin synthesized in the central nervous system to a specific antigen and that isolated gamma_2 globulins are related to the etiology of these diseases. To gather evidence to support these hypotheses, experiments are now under way to determine whether the isolated

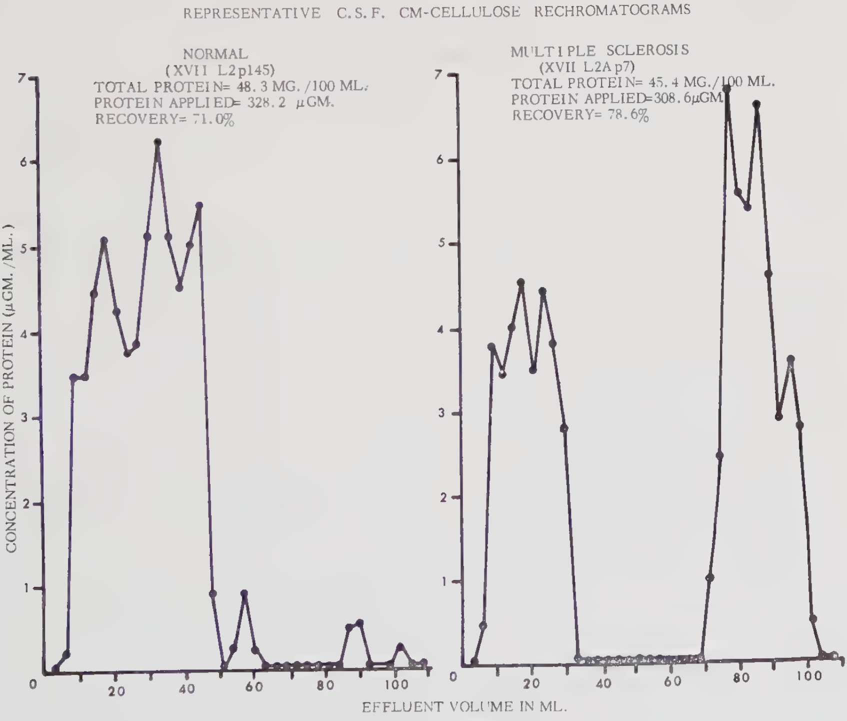

Fig. 1. (From Tourtellotte, W. W., et al.: Ztschr. Immunitätsforsch. [in press] 1963.[22])

gamma_2 globulins contain specific antibodies, such as anti-white matter or anti-Treponema pallidum, in multiple sclerosis and in neurosyphilis, respectively.[23]

White Cells

A study of white cells in the spinal fluid from patients with multiple sclerosis is also under way in our laboratory.[21] This study seemed advisable since an increase in the white cell count correlated frequently with the clinical activity (see Table 1).

In general, our studies have confirmed those in the literature.[21] The pleocytosis rarely exceeds 50 white cells per cu. mm and it is due to small lymphocytes. To find 0.5 per cent polymorphonuclear cells in the spinal fluid of a patient to whom we have given a diagnosis of definite clinical multiple sclerosis is rare. It is our experience that, if a patient has a significant percentage of polymorphonuclears in his spinal fluid, he does not have multiple sclerosis or he has multiple sclerosis and another disease.

We have found a positive correlation between the white cell count and the gamma_2 globulin in the spinal fluid. This has suggested to us that the small lymphocytes may be synthesizing gamma_2 globulin.

Could it be that the increase of white cells in the spinal fluid is related to the etiology of multiple sclerosis? Perhaps the spinal fluid white cells are produced in areas of demyelination and subsequently find their way into the fluid. Under these circumstances they may carry something related to the pathogenesis, for example antigen or antibody.

Lipids

Since the cerebrospinal fluid is in close contact with the brain, whose lipid content is high and whose lipid profile is unique, it is possible that disease of lipid metabolism of the brain could be reflected in the lipid profile of the fluid. This is a particularly attractive hypothesis in the case of multiple sclerosis, in which plaques of demyelination are frequent in the periventricular area.

In a previous communication[20] on spinal fluid lipid profiles in various diseases, including definite clinical multiple sclerosis, we reported that the total phospholipids were decreased probably because of a decrease in lecithins and that the nonphosphorus sphingolipids which included cerebrosides were increased. Because the total cholesterol was decreased and the free cholesterol remained the same, the percentage of free cholesterol was increased. The same lipid profile was discovered in patients in either a relapse or remission. Furthermore, in patients with acute retrobulbar neuritis and no other neurological manifestations to suggest multiple sclerosis, only lecithins and total cholesterol were found significantly lower.

The lipid data are expressed in another way in the table, that is, as the percentage of patients with a diagnosis of definite clinical multiple sclerosis in remission or in relapse who have increased or decreased cerebrospinal fluid components. Fluid components are listed in the order of increased incidence of abnormality. This table illustrates several significant points. Of all the fluid components studied, gamma_2 globulin is the most often abnormal; and the incidence of abnormality is not increased by a relapse. The next most abnormal fluid component is total sphingolipids; this is due more to increased nonphosphorus sphingolipids than to increased sphingomyelin. It is interesting to note that approximately the same number of patients have elevated lecithins as decreased lecithins; this affects the total phospholipids especially in relapses, in which almost as many patients have decreased values as increased.

It should be pointed out again that the only component which we have found to reflect the relapse of multiple sclerosis is the white cell count of the cerebrospinal fluid.

Behavior of spinal lipids in multiple sclerosis was also studied by Plum.[10] He stated that there is clearly a pronounced increase of cholesterol in the fluid, probably due to free cholesterol. In previous reports we have discussed the difficulties encountered in the determination of cholesterol in dilute solutions,[15, 18] and perhaps these difficulties explain the difference in results reported from his laboratory and ours.

McArdle and Zilkha[9] have recently reported an excellent study on spinal fluid phospholipids isolated from 31 patients with multiple sclerosis. Their normal values agreed well with those previously reported by us, and the results obtained in their patient group and in ours might be in closer agreement if they had expressed their results in terms of milligrams of protein per 100 ml. or of lipids per milligram of gamma_2 globulin-free cerebrospinal fluid protein, since other studies done by us indicate a relationship between lipids and proteins.[1, 15, 16, 17, 20]

Recent studies done by Tuna, Logothetis and Kammereck[25] showed that fatty acids obtained from sera and spinal fluid of a few patients with multiple sclerosis differed from normal. Plum[10] recently reported a study on spinal fluid lipoproteins using a paper electrophoretic technique, in which the pattern in multiple sclerosis deviated very much from normal findings.

Our studies and those reported in the literature leave only slight doubt that changes occur in the spinal fluid lipid content of patients with multiple sclerosis. The suggestion is made that breakdown products of nervous tissue, and possibly myelin, appear in the cerebrospinal fluid.

Blood-Cerebrospinal Fluid Barrier

A recent study by Bornstein[3] has shown that a high percentage of patients with multiple sclerosis have a factor in their sera which demyelinates a myelin tissue culture. If this factor is involved in the pathogenesis of multiple sclerosis, it must be able to pass into the brain. Perhaps a relapse or a chronic progressive course in multiple sclerosis is related to a decrease in the blood-brain or cerebrospinal fluid barrier.

In order to test the possibility of an abnormality in the blood-cerebrospinal fluid barrier, sodium bromide was given to 20 normal persons and to 73 patients with multiple sclerosis.[6] The data indicated that a significant lowering of the barrier existed in the following situations: (1) chronic multiple sclerosis with disease duration over 10 years; (2) chronic progressive multiple sclerosis with a deteriorating course over two years; (3) a bout of multiple sclerosis when not improving; and (4) total disability in the Kurtzke scale of 5 or more. These data indicate that bromide ion can penetrate into the spinal fluid more easily in certain clinical manifestations of multiple sclerosis than in normal individuals.

It also might be possible to test the blood-brain barrier. Sodium bromide could be given to patients with multiple sclerosis who have not long to live. Postmortem analyses of the brains of these patients for bromides of various areas, especially plaques, could be carried out in the manner described elsewhere.[19] This approach may bring us a step closer to the answer of whether the blood-brain barrier is disturbed in patients with multiple sclerosis.

SUMMARY

Fifty per cent of patients with a diagnosis of definite clinical multiple sclerosis have a cerebrospinal fluid syndrome characterized as follows: an elevated percentage of gamma$_2$ globulin immunochemically determined, negative serological test for syphilis in a patient who has not had syphilis, a total protein concentration less than 100 mg. per 100 ml., a normal serum gamma$_2$ globulin concentration, and a leukocyte count of < 50 cells per cu. mm. composed of < 0.5 per cent polymorphonuclear cells and mostly mononuclear cells (small $>$ large lymphocytes and monocytes.)

The colloidal (gold and gum mastic) and zinc sulfate tests, which have been proved not to be tests for gamma$_2$ globulin, are elevated in 25 and 75 per cent respectively of a group of patients with definite clinical multiple sclerosis.

Immediately after an acute exacerbation of the signs and symptoms of multiple sclerosis the spinal fluid white cell count may become elevated or further elevated. In remission 29 per cent of patients can be expected to have an elevated white cell count (> 4.7 white cells per cu. mm.); on the other hand, 60 per cent of patients in relapse can be expected to have an elevated cell count.

Immunoglobulins, white cells and lipids in the spinal fluid of patients with multiple sclerosis, as well as the movement of bromide ion from the blood into the cerebrospinal fluid, were discussed. The author believes these to be the most likely cerebrospinal areas in which new

information about the pathogenesis of multiple sclerosis may be discovered.

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Traumatic Paralysis: Diagnosis and Nonsurgical Management

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THE PARALYSIS which follows a traumatic experience may be the result of implication of the brain, the spinal cord, the peripheral nerves, the autonomic nervous system or any combination of these. Or the involvement may be functional, alone or combined with any of the above. The disability may come on immediately or some time after the trauma, or the paralysis may be transient. Finally, a person already paralyzed in part may be involved in an accident; e.g., a child with a so-called cerebral palsy or an adult with a hemiplegia, paraplegia or parkinsonian state is more prone to injury on stairs, on pavements or in traffic. Therefore, when the patient is first seen, it is essential to obtain as complete a history as possible about what occurred and about the patient's previous state. The latter may require careful and discrete screening in these days of medicolegally-oriented people.

ACUTE STAGE

MISCELLANEOUS CONSIDERATIONS

If the patient is seen immediately after trauma, he may not be moving much because of traumatic shock, or parts may be immobilized because of local injury to soft tissue and bone. Behind the surgical shock may be neural shock, diaschisis,[26] with loss of function. The initial neurological examination is therefore set in the framework of the general evaluation, in which the emphasis is on vital signs like those of the respiratory and circulatory system, the detection of fractures, hemorrhage and the like. Treatment is similarly directed to these fundamental problems. Should convulsions be part of the initial picture, measures must be instituted promptly to prevent further injury to tongue and limbs. Obstruction of the airway by the tongue or by secretions needs attention. However, as soon as the patient's general condition permits, a careful neurological evaluation should follow; one should note the state of consciousness, paralysis or paresis, the presence of pathological reflexes both plantar and hand, cranial nerve signs, particularly the size and reactivity of the pupils and the condition of the optic nerve heads. All of this must be carefully recorded with notations as to movement, flaccidity or spasticity of the part, and if the patient is responsive, evidence of sensory deficits. The findings must be correlated with those of the general examination, e.g., the presence of a depressed skull fracture, bleeding from the ears or nose, a back injury or a limb fracture.

It is essential that the initial screening be total or as nearly complete as possible under the circumstances. If the examination must be made on a street, in a field, at a construction site or in a home, only sufficient survey is needed to determine the essential pathologic condition and the state of shock. As soon as these permit, the person should be transferred to a hospital or a setting where the more detailed examination may be carried out.

Transportation

Experience in World War II has indicated that once surgical shock is relieved, the patient with a head injury may be transported safely to a center where adequate care is available. This includes even airplane and helicopter carry, as for construction and mine workers in outlying regions. The cruising level is kept below 5000 feet unless a pressurized cabin or oxygen is available. Those with spinal cord injuries may similarly be carried; where no litter is available, a broad plank or door may be used. A truck or station wagon is preferable for transporting a person with a spinal cord injury. Casts are to be avoided in the transport, but fractured limbs may be splinted so as not to increase the injury.

Drugs

Drugs are best avoided at this point. Morphine is contraindicated in the presence of head and brain injury. Demerol may be used if root pain or pain from fractures or lacerations is severe. Usually careful handling and splinting reduce the need to a minimum.

General

Before transport, the patient's pockets should be emptied and blankets and sheets drawn absolutely smooth to avoid decubitation. Crucial areas should be padded: sacrum, ischiae, trochanters and heels for the supine patient, and forehead and knees for the prone.

At the hospital the more detailed neurological examination follows. This includes evaluation of temperature, bladder and rectal function. Unless there is contraindication from surgical shock, the patient may be carefully moved to the x-ray department for spine and/or long bone studies as the case may require. Skull x-rays are best postponed unless a depressed fracture is suspected; later when the patient's condition has improved and he can cooperate, these studies may be made. X-ray studies may quickly determine the presence of a pineal shift as in subdural or epidural hemorrhage, a depressed area, or indirect fragments in skull or spine which merit surgical consideration.

Spinal Puncture

If only skull injury exists, there is little to be learned early from cerebrospinal fluid studies, and even in a case of spinal injury, no procedures are initiated while the patient is in surgical shock.

In spinal cord injury the presence of a block is important to determine and the question of laminectomy becomes paramount. This problem is far from an easy solution. Some claim that in the absence of a spinal block the neural structures are not seriously compressed; others believe that when block is present early laminectomy offers the patient some chance of improvement. Most of the controlled studies argue against laminectomy. In Comarr's[6] series, 16 per cent with and 29 per cent without laminectomy showed improvement. In our study of Korean War casualties,[4] 19.6 per cent of the early laminectomized patients went on to some recovery, but in our World War II paraplegics,[19] generally not operated upon, or operated upon late, the rate of some recovery of function was 24.6 per cent. Unless a surgeon skilled in spinal cord work is available, it is best to lean toward nonsurgical treatment. In cervical spine dislocations, the indications are for skeletal traction.

In the presence of block, if the clinical symptoms advance rapidly, early laminectomy may be considered, but the procedure is always utilized for the presence of bone fragments or foreign bodies in the spinal canal[23] or for severe root pain.[13]

CRANIOCEREBRAL INJURY WITH PARALYSIS

An airway must be maintained with tracheotomy and oxygen when needed. Fluids are given to combat shock and maintain osmotic homeostasis;[9, 15] 2000 to 2500 ml. may be administered, some as 10 per cent dextrose to reduce tissue edema. Control is maintained by check on blood electrolytes. Hyperthermia must be controlled by means of ice bags, sponge baths, amidopyrine, chlorpromazine and ice water enemas. Mansuy and LeCuire[12] and Wertheimer and Chevalier[29] have reported definite improvement in mortality and morbidity of severely injured patients treated with hypothermia. The post-traumatic sequelae, neural and functional, appear to be reduced when the tissue temperature is brought down to a level more consistent with the relative hypoxia of the injured state.

The increased intracranial pressure may be reduced by use of urea intravenously[10] or by the rectal administration of 200 to 400 ml. of a

50 per cent magnesium sulfate solution by the drip method. The urea administration apparently prevents the secondary rise seen after hypertonic sucrose and glucose. Lumbar cerebrospinal fluid drainage is of value in carefully selected cases, but is not without its dangers from herniation of the cerebellar tonsils into the foramen magnum or of the hippocampal gyrus into the tentorial incisura. Sometimes the careful, slow removal of a small amount of fluid is followed by a disproportionate immediate improvement. It would seem that suddenly the intracranial hydrodyanmics become compensated, perhaps with restoration of circulation of both blood and cerebrospinal fluid. The nature of the physics of flow and of elasticity of intracranial contents would justify such a hypothesis.[2, 18]

Restlessness is best controlled without drugs. Emptying the distended bladder or feces-packed rectum and changing urine-soaked rumpled bed sheets may be all that is required. A quiet room and a calm competent nurse are the best sedative. Restraints are to be avoided. Convulsions are treated with parenteral dilantin sodium, paraldehyde or, if needed, intravenous sodium amytal or intramuscular sodium phenobarbital. The paralyzed limb or limbs are splinted and put through complete range of movement several times each day unless long bone fractures interdict.

SPINAL CORD INJURY

The same principles apply as for head injury. The essential care in the acute period consists of good nursing attention, a quiet room, dry, smooth bedsheets, and changing of position to avoid pressure particularly at bony points. Attention to bladder and rectum is essential. Casts are to be avoided. The limbs should be splinted and put through a normal range of motion several times each day. Nutrition and general medical care are kept at an optimum.

PERIPHERAL NERVE AND AUTONOMIC NERVOUS SYSTEM

Again the principles previously enumerated obtain, but a new factor enters here—pain. This is particularly true when the median or posterior tibial nerve is involved, or when the neural elements, from root through plexus, which contribute to the formation of these nerves are implicated. Causalgic pain may appear early, even in nerves which are represented peripherally in the ulnar or peroneal distribution. The patient complains of a hot, burning extremity and cannot tolerate the touch of bed sheets. A cradle over the limb is often nexessary, but more important, one must be on the alert immediately against the setting up of a drug dependency or addiction. A consistent course of kind but firm avoidance of the opiates, Demerol and even barbiturates is needed.

The last are constantly demanded for sleep. Early physical therapy, sympathetic blocks when indicated, and setting the rehabilitation blue print for the rapid removal of the patient from a dependent hospital atmosphere are good prophylactic measures. Combinations of injury to any two or three of the above neural systems may occur. Thus, a combined craniocerebral and spinal lesion is often seen, or a spinal cord-plexus problem.

Paralysis during Acute Phase

This may be a direct result of a progressive pathologic condition in the neural tissue, brain, spinal cord, peripheral or autonomic nerve, or it may be the manifestations of neural shock. In man, neural shock may last for several weeks, particularly after a spinal cord lesion; then recovery begins. The peripheral, disconnected spinal cord segment begins to assert the neural activity residual within itself.[3] Therefore, it is essential that repeated neurological and ancillary laboratory examinations be an integral part of the management of the acute phase and later of the transitional and chronic periods. A traumatic hemiplegia may begin to resolve after several days, or a paraplegic state may recede after weeks or even months. The stage of reduced reflex and sensory response of the neural shock period is gradually replaced by one of reflex return. The pathological reflexes at the planta (Babinski and others) and hand (Hoffmann) may fade as the normal flexion response comes in. With this, a return of sensation may ensue, in varying patterns, depending on whether the pathologic condition is in the brain or spinal cord. The same course may follow if a peripheral nerve has been transiently injured.

In case of brain injury, the electroencephalogram is of value. The dysrhythmia of the immediate post-traumatic period gradually lessons as the brain recovers, and successive electroencephalograms are usually made to follow the clinical progress. If a subdural hematoma is forming, the electroencephalogram may show increasing disturbance and may offer an important clue to newly evolving conditions.

In peripheral nerve damage, the procedures of electromyography, chronaxiometry, strength duration curves, tetanus ratio and nerve conduction velocities can give important evidence if the nerve is partially or completely interrupted and if recovery is taking place. It is essential therefore to establish a baseline in the acute phase to determine the direction of the process. Often the electrical signs precede the return of actual function.

It is important, during the acute phase, to learn as much as possible about the circumstances of the accident and the personality of the patient. The nature of the disability which is seen in the chronic period is related not only to the anatomical damage to neural elements with resultant paralysis, but also to the psychological makeup of the injured person. The later picture is a result of a dynamic interaction of the two so that the total disability far transcends that which one would expect in impairment from actual paralysis.

TRANSITIONAL STAGE

This intermediate period is one of transition from the acute to the chronic phase. Vital functions have now returned, and the general trend is for restitution of function. The sensorium of the patient with head injury begins to clear, and mild paralyses begin to recede. Convulsive seizures are more likely to be under control; the EEG shows improvement. Patients with partial lesions of the spinal cord begin to experience a lessening of the paralysis, and partial function may begin to return to one or another limb. The rectum and later the bladder may come under voluntary regulation. The sensory defect may show some recession in one or more modalities of sensation, such as a lessening of the anesthetic and analgesic areas. The return of feeling may come along successive superior dermatomes or may start in the saddle area. There is no consistent pattern.

The patient with a severe lesion may see the beginning of return of automatic, reflex activity to the distal spinal cord segment. Pathological and withdrawal reflexes may make their appearance, plus early mass responses.

The same holds true for peripheral nerve lesions. Motor and sensory defects may lessen, and the electrical signs may show improvement The lengthened chronaxie may shorten, the strength duration curve may flatten and conduction velocities may become greater.

However, the trend may also be toward worsening. The patient with craniocerebral injury may become duller, irritable, sleepy, forgetful or confused. A paralysis may worsen or more disability may set in as the subdural hematoma or the cystic hygroma forms. The electroencephalogram worsens, with slowing and aberrant wave formation. A patient with a spinal cord lesion may have an upward extension of the paralytic and sensory level because of ascending thrombosis of the spinal cord vessels. Or a person with a peripheral nerve lesion may show increasing disability as a nerve that had been previously mildly affected becomes implicated between bone fragments, in callus formation or in scar.

Last but not least, after the patient has recovered from traumatic shock and has a chance to assess his actual or apparent disability, the psychological aspects of the problem become manifest. Thus a man, finding himself hemiplegic, aphasic, paraplegic, monoplegic, impotent, anesthetic or the like becomes acutely disturbed. A depression is not uncommon, frequently followed by a chronic anxiety state. The latter may be the precursor of a very disabling after-period.

It is incumbent upon the managing physician to make repeated examinations with careful recording. Yet such reviews must be performed in such a way as not to offer a nidus around which an anxiety state will grow. He must be prepared to move in on the forming hematoma or the paralyzing callus.

The actual management consists of early physical therapy, first in the patient's bed, then in the physical therapy department. Early removal from bed is encouraged and the patient is rapidly re-introduced to daily life activities, from self-care to newspapers, books, television, radio and visitors. A goal-directed program must be set up early to return the person to his home and, if at all possible, to some gainful employment. It is never too soon to set up a realistic goal, not to tell the hemiplegic or paraplegic that he will walk normally again, but to instruct him how he must help in the reparative process to bring about optimum recovery. The plan is rehabilitation, not repeated ritualistic heat lamps and massage which often are "make work" measures.

It is at this point also that one must be alert to the dependent personality who is fertile soil for the post-traumatic neurosis. He must be encouraged to become active to the fullest extent and made to help himself.

THE CHRONIC STATE

This is a period which gradually sets in after the transitional stage. The paralysis and sensory deficits are well established and it is possible now to set up a plan for long-continuing care.

CRANIOCEREBRAL INJURIES

Wartime experience has completely revolutionized our ideas of the treatment of craniocerebral injuries. The traditional use of rest and quiet has been completely discarded for a program of gradual physical exercise as soon as the patient's general condition permits.[5, 20–22] The common previously limiting symptoms of vascular instability, headache, sensitivity to head movements and pain about the eyes are not treated by avoiding the aggravating factor but by encouraging the very activities which bring the related parts into action. Thus stooping, bending and orthoptic exercises are encouraged. Early return to work, if possible the person's own, or closely related, is tried, but the patient must be prepared for early failures (Tables 1 and 2).

Post-traumatic Seizures

These may develop, particularly in a paralyzed side (jacksonian), usually 6 to 18 months after injury. The described incidence is 25 to 40 per cent, depending on the severity of the lesion, and may rise to 50 per cent if the dura had originally been penetrated.[14] The electroencephalogram is valuable in informing the observer of the evolving

Table 1. Prognosis of 237 Acute Cases of Head Injury in Service Personnel Based on Follow-Up Report After Return to Duty*

DURATION OF POST-TRAUMATIC AMNESIA	TOTAL NUMBER OF CASES IN GROUP	PERCENTAGE OF CASES IN EACH GROUP SHOWING A SUCCESSFUL RETURN TO DUTY
None	28	89
Under 1 hr.	75	89
1–24 hr.	65	88
1–7 days	34	76
Over 7 days	35	40
	237	80

* From Symonds, C. P., and Russell, W. R.: Accidental head injuries prognosis in service patients. Lancet *1:* 7, 1943.

epileptic focus. Walker[27] has shown that the electrical manifestations of traumatic epilepsy are to be found in the normal cortex adjacent to the cerebral scar and not in the obviously damaged area.

Anticonvulsants are administered prophylactically in instances, if on the side of the skull contralateral to the paralyzed side the electroencephalographic findings persist or become worse over a period of months to years. Unfortunately, surgical excision of this scarred area, in admittedly more severe cases, does not offer a very good outlook. Less than 50 per cent of such patients become free of seizures, and all must be given medication for two or more years after surgery even if there are no convulsions.

The residual paralysis after craniocerebral injury is usually single or double hemiplegia, with or without aphasia. The hemiplegic state may vary from person to person, but generally there is spasticity which involves chiefly the abductors and flexors of the upper limbs and extensors and abductors of the lower. The deep reflexes are hyperactive and there are pathological toe signs like the Babinski. The process of recovery is a constantly evolving series of reactions which form a pattern, sometimes with variation.[24] Voluntary motion returns first as flexion at the shoulders and hips, later as flexion of the elbow, wrists and fingers, and finally of knee and ankle. Any attempt at willed movement results in flexion synergias or combined flexor movements throughout the upper or lower extremities. Contractures of the hands, elbows and tendo Achilles may set in.

Physical therapy should be started in the acute state and carried on throughout the transitional period to reduce the spasticity and to prevent contractures. Now the passive movements are merged with sitting up in bed and standing procedures. The latter may be started between the fourth and seventh days. Standing also has psychological benefit because it tends to dispel the patient's idea that he is helpless. Rope-and-pulley exercises of the in-bed state are merged into self-care activities such as feeding, washing and dressing.

Expressive aphasia retraining also starts early and should be pursued intensively, particularly with the aid of a trained speech therapist.[28]

Hemiplegia following trauma affects a younger age group than that after cerebrovascular accidents. The recovery rate is therefore even higher than in the latter; 85 to 90 per cent may be able to walk and take care of themselves and over 30 per cent will be gainfully employed.[1, 11] The aphasic patient may be tested for ability to speak after intravenous injection of sodium amytal, which relieves the anxiety attendant to the early frustrating attempts at language. This is reassuring to the affected person.

The syndrome of denial of the paralyzed part (anosognosia) or other cortical sensory (parietal lobe) defects makes the rehabilitative process exceedingly difficult since the patient cannot cooperate well in the retraining process. Confusion, depression, irritability, dependency and medico-legal aspects all contribute to the hurdles which must be overcome. Yet the effort must continue persistently and progressively. This may require a so-called team consisting of attending physician, physiatrist, nurse, physical therapist or rehabilitation person, and often a social worker, who brings the family into the picture and helps them to play their role in the rehabilitation process. In addition to the physical therapy, recreation and social contacts are encouraged. If where the

Table 2. Duration of Incapacity for Full Work in an Unselected Group of 139 Working Men and Women Admitted to Edinburgh Royal Infirmary (Cases Arranged According to Duration of Post-traumatic Amnesia) *

PERIOD OFF FULL WORK	DURATION OF POST-TRAUMATIC AMNESIA				
	Under 1 hour	1–24 hr.	1–3 days	over 3 days	Total number of cases in group
Under 2 mo.	37	30	2	4	73
2–6 mo.	11	8	3	15	37
6–18 mo.	4	3	—	3	10
Over 18 mo.	9†	4	—	6	19
Total	61	45	5	28	139

* From Russell, W. R.: Studies on head injury. Brit. M. Bull. *10:* 65, 1954.

† In seven of these nine cases there was a compensation problem outstanding.

impairment will obviously require change of job, occupational retraining is started early.

The spasticity usually yields in part to the physical therapy measures, but some have advocated the use of drugs like Myanesin and zoxazolamine (Flexin). I have never seen any beneficial results from these substances.

Some patients may require temporary or permanent braces for the lower extremities but these should not be ordered under three months after the injury, when it becomes apparent that the muscles will not be able to hold up body weight. Splints for the upper extremities to prevent contractures are of value but should permit exercise, like with a rubber ball.

Early the concentration is on the lower limb to restore walking, but the more difficult-to-rehabilitate upper extremity should not be neglected. Fine finger movements may never return. Certain realistic limits for treatment must be set. Usually there is some response in four to six months, but in some cases the treatment may properly be continued up to 18 months.

Chronic pain syndromes may develop, associated with fixation of shoulder and arm and may interfere with rehabilitation. They are best prevented by early passive and active motion. Spontaneous pain due to thalamic injury is exceedingly difficult to treat.

The Post-traumatic Syndrome

This all too common sequel interferes with the care of the patient with paralysis after craniocerebral injury. The picture is that of headache, dizziness, insomnia, irritability, inability to concentrate, hyperhidrosis, depression and personality change. It appears in 35 to 40 per cent of patients who have suffered a major or minor head injury. Severity of trauma plays no role and all investigations point to the pretraumatic personality. Some symptoms are iatrogenically produced by the oversolicitous physician who hovers over the patient's every move. Unnecessary cervical collars, splints and immobilization add to the person's concept of being helpless. The myth of the brain being a "delicate organ which must be protected" is frightening to the patient. Again the British experience of World War II is noted, that early removal from bed, early ambulation and early return to some gainful employment are mandatory. Medico-legal complications are a stumbling block to cooperation in therapy. Small symptoms are reviewed again and again by the lawyer as he builds up his brief to assure a larger settlement. The reiteration of "We can't settle until we know what will happen later" sows doubt in the patient's mind that he is really improving. The long delay from clogged court dockets results in many years' postponement of the settlement. Meanwhile the incapacity becomes static and remains even after the suit is closed; the settlement is small compensation for the often permanent functional disability.

All therapy must be directed toward the total situation, not only the actual paralysis, but toward the medico-legal and socio-economic factors.

SPINAL CORD PARALYSIS

The care a patient with spinal cord injury and paralysis, usually a paraplegic, is a long-term project and involves not only the treatment of the disabled limbs, but also the attendant complications of these conditions. The lessons learned since World War II and the Korean conflict have brought about a new set of measures for the rehabilitation of such patients. Yet one must keep in mind that not every paraplegic patient will walk, or that if he walks he will rarely walk unaided. Usually he will walk with canes, more often with braces and crutches, or he may be dependent on a wheel chair. However, he will probably not be bedbound; he will be able to drive his car and to return to a nonhospital world where he may sometimes work at gainful employment and have a family life. None of these achievements come easily. They are the end-product of better understanding of spinal cord physiology, control of infections, appreciation of the role of nutrition and recognition of the significance of psychological factors. Disciplines brought to bear in the rehabilitation process include the neurologist, the physiatrist, the genito-urinary, plastic, orthopedic and neurological surgeons, the internist, the psychiatrist, the psychologist, the physical, occupational, recreational therapists, the social worker, nurses and ward personnel, who perforce must live with the patient and who must minister to his every need, be it physical or emotional. In the case of a person not in the armed services, the family physician often must play many roles.

Physical therapy has already been started in the acute stage, has been carried out through the transitional period and now enters the chronic, long-term phase. Exercises to build up muscles which will require extra use are established, particularly those of the arms and shoulders, which will be utilized by the patient for lifting himself in and out of bed. Spastic limbs may relax in a Hubbard tank or therapeutic pool. Swimming is helpful and psychologically important because it allows the paraplegic patient to move at will without aid. Corrective therapy aims at improving muscle power through the use of dumbbells, weights, pulleys, and mat and short crutch exercises (Fig. 1). The patient is taught to transfer himself unaided from wheelchair to mat. Quadriplegics are trained in trick movements, the remaining muscles being aided by special appliances to hold a razor, a comb, a toothbrush and eating utensils (Fig. 2). Sports, including swimming, bag-punching and limited wheelchair basketball, have their value.

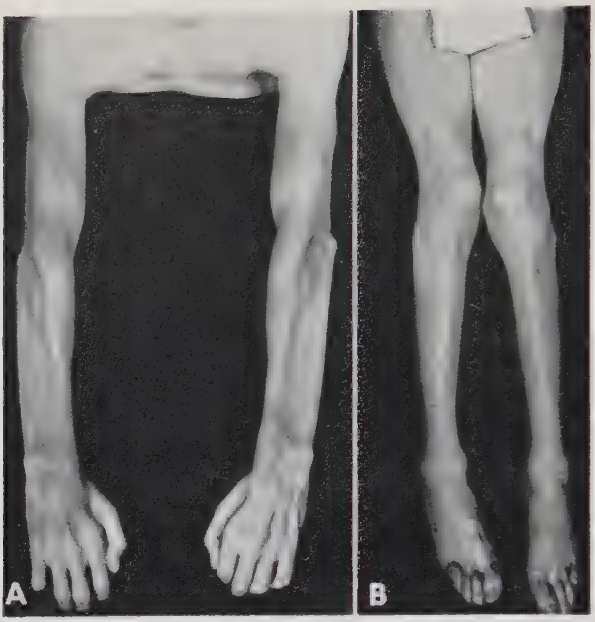

Fig. 1. Muscle atrophy in spinal cord lesions. *A*, Nuclear and root atrophy. *B*, Upper motor neuron atrophy.

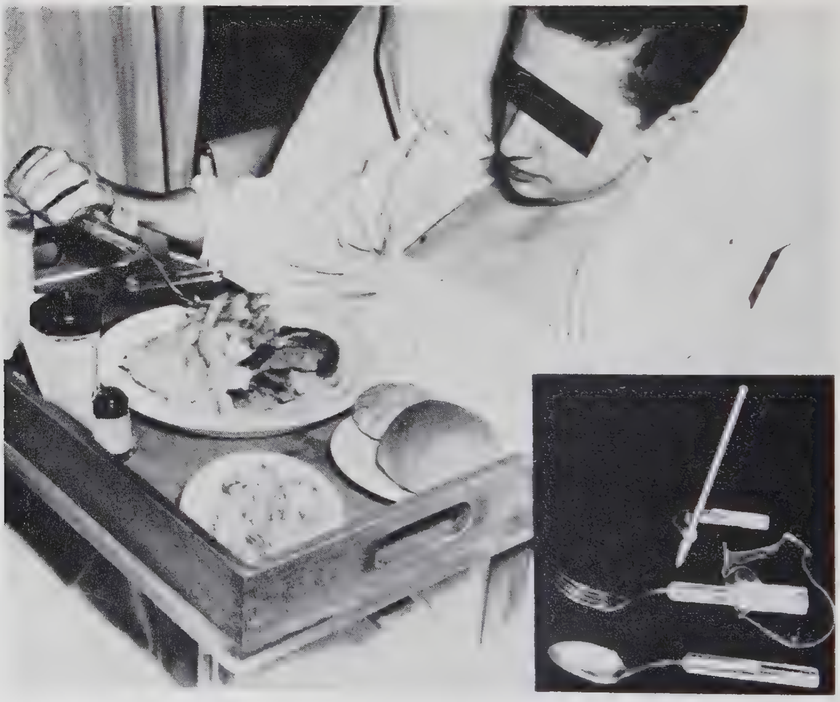

Fig. 2. Quadriplegia. Devices for eating.

Ambulation is started with perparation of shoulder and trunk muscles for weight bearing. Munro reports that 98 per cent of patients with cauda equina lesions, 49 per cent with transected spinal cords and 56 per cent with partial spinal cord lesions can learn to walk.[16] Braces aid in the process, as do balancing exercises between parallel bars and in the walker. Ambulation may be started with crutches, four-point gait if there is individual limb control, and three-point if there is none. Patients with lesions below D-10 can learn the former; most prefer a four-point gait when it is possible. Patients are taught to traverse even ground, curbs and stairs, to get in and out of wheelchairs, beds and cars, to sit down and get up from chairs and toilet seats, to bathe and to get into and out of clothes and braces.

One also must be prepared to treat the attendant problems. Decubitus ulcers can be produced by a pressure of as little as 50 to 60 millimeters of mercury over a period of 6 to 12 hours[8] (Fig. 3). Patients must be

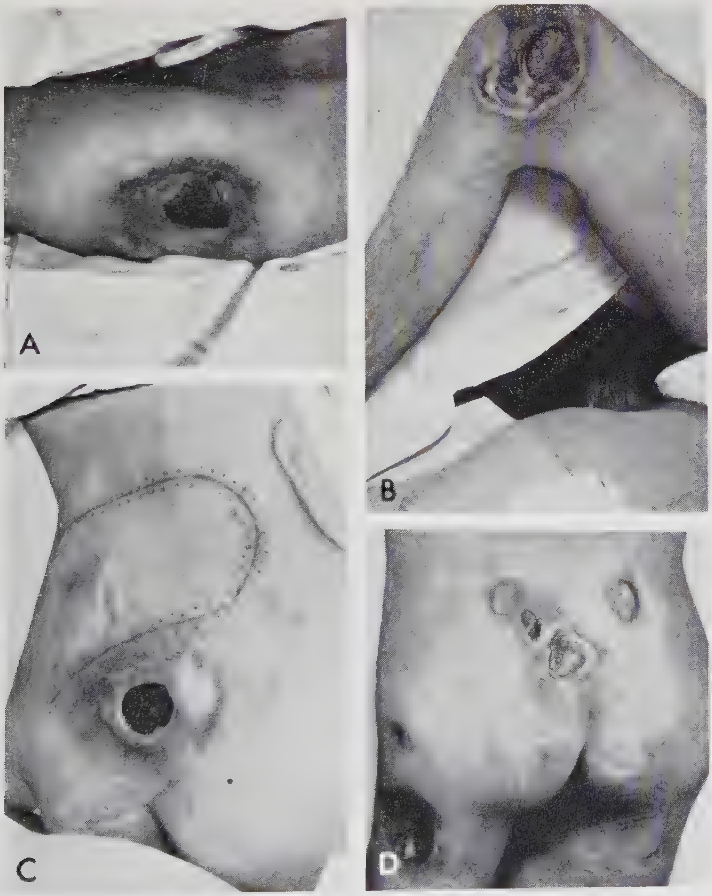

Fig. 3. Decubiti. *A*, Trochanter; *B*, knee; *C*, sacral; *D*, multiple.

kept off pressure points such as the sacrum or trochanter by being turned every two hours. Dry, smooth sheets are essential. These measures can prevent a large percentage of the decubiti. An early skin breakdown may be cleared up by scrubbing the wound with soap and water and removing the pressure. A large defect may require plastic surgery.

Genitourinary care is needed for every patient and constitutes a chapter in itself. Infections of this area are the most common cause of death in patients with a traumatic paralysis of the spinal cord. The ultimate objective of treatment is an automatic bladder with 24-hour control, and this may be achieved in a high percentage of patients. Bowel care similarly is aimed toward the removal of the need for enemas and toward establishing a reflex type of evacuation. Using such training, Pollock and his co-workers[19] were able to effect patient-controlled defecation in 91 per cent of 244 paraplegics studied.

Spasms set in during the chronic state, anywhere from two weeks to seven months after the injury as reflex activity returns to the isolated distal spinal cord segment. These new reflexes are defense synergias set off by midline or lateral stimuli. They may be flexor, extensor, adductor, unilateral, bilateral or alternate. They may be so severe as to interfere with healing bedsores. They complicate genitourinary care and retard rehabilitation. They may even cause fractures and dislocations. These spasms seem to reach a peak in the second year and then subside. Such reflex activity is not spontaneous but is a product of the afferent volleys from the irritated areas, decubiti, osteomyelitis, infected catheters or bladder. Eliminating these incoming stimuli will prevent the spasms. In contrast, the constant firing into the released isolated segment causes the limb to draw up in flexion, producing a so-called paraplegia-in-flexion which militates against any attempt to rehabilitate the paralyzed person (Fig. 4). Drugs are useless for these spasms, and anterior rhizotomy may become necessary. However, the more effective the prophylactic care of decubitation and genitourinary infection, the less the need for rhizotomy. Sometimes absolute alcohol injection into the subarachnoid space, 10 to 15 milliliters, will relieve the spasms.

Pain may also interfere with rehabilitation and may be of the root type, but more often it is an intense tingling below the lesion. This cannot be localized. The natural history is that the pain tends to diminish toward the end of the first or second year. It is important that these patients not be given addicting drugs like narcotics or barbiturates.

The general medical problems are attended to, particularly the loss of nutrition, the electrolyte and blood protein disturbances. Psychological support of the patient is paramount. Such persons become depressed and occasionally are suicidal, particularly in the transitional and early chronic state. They become discouraged by events in their families, are submerged by economic difficulties, emotional disturbances in the children, or infidelity on the part of their spouses. All of these interfere

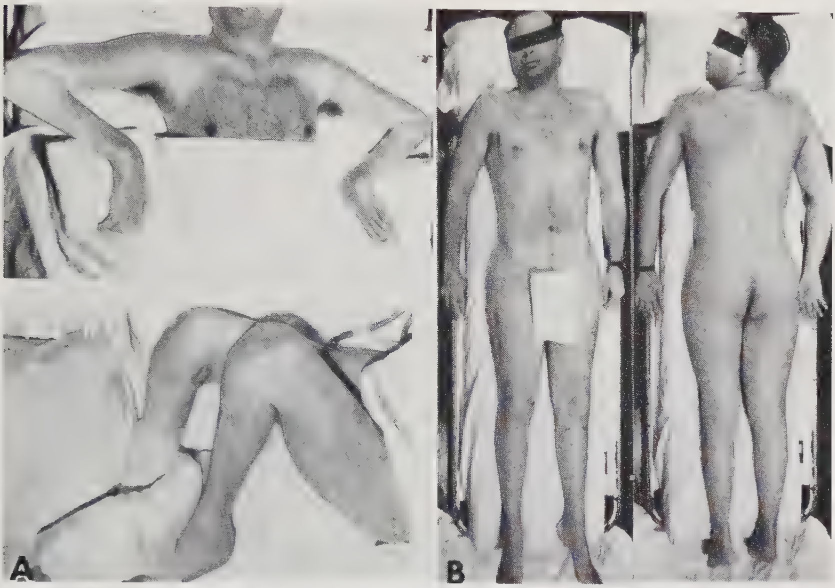

Fig. 4. The changing picture. *A*, Paraplegia in flexion; C-5; physiologically complete. *B*, Paraplegia in extension; D-6; anatomically complete.

with the restoration measures. This is why the social worker and psychiatrist play so important a role in the continued rehabilitation of the person paralyzed by spinal cord injury.

PERIPHERAL NERVE PARALYSIS

Patients who have had mild transitional lesions of peripheral nerves usually have recovered after several weeks, but those who have had more severe injuries usually move into the chronic phase. Sometimes lesions have required primary or secondary suture but now the nonsurgical phase is considered.

The results of long-term treatment are often not exclusively related to the grade and degree of restoration of motor and sensory function but to the patient's ability to return to a full and useful life. Bowden[17] differentiates between "academic and functional recovery." He emphasizes the distinction between the regrowth of nerve fibers and the return of function. He points out that recovery means restoration of the mechanism of neural transmission. The long-term effect of the injury on bone, joints and soft tissues, especially blood vessels, must also be considered. What has been the impact of the nerve injury on the patient's life? Of what symbolic significance is the injury? What has it meant to him in terms of employment? Does he look upon himself as a complete or incomplete person, forever handicapped? The incentive to recovery is important in the realistic evaluation of the goal of treatment. Disability benefits, pensions and compensation play a significant role. Participation in therapy, in sports and even in employment is sometimes half-hearted if there is a possibility that the benefits that accrue from this injury may be reduced because of improved function of the injured parts. This is particularly true when there is a likelihood of a permanent residual defect. Therefore it is essential that law suits be settled or compensation established so that the patient may pursue the goal of optimum recovery without emotional conflict. Supportive psychotherapy is often of great aid to these patients and may also involve treatment of selected members of the family.

The actual treatment of the motor defect consists of the usual physical therapy measures—heat, massage, passive exercise, and as soon as there is motion, implementing of these movements by floating the limb in water, movement on a dry, powdered board, and later against resistance. The benefits of electrotherapy have never been clearly established. Some claim that patients do well on electrical stimulation; others believe that it increases fibrosis in weak muscles. One must keep in mind that the ingrowing nerve moves down along its channel at the usual rate of about 1 inch per month and that even when it reaches the intended muscle, a certain "maturation" must take place so that the muscle begins to utilize the neural impulses which now reach it.

Electrical reactions are useful in determining the restitution of the neural pathway. The high chronaxie drops, the tetanus ratio begins to return to its former 4–1 range, the strength duration curve loses its steepness and begins to become more flattened. On electromyography the fibrillary potentials of denervation begin to drop out and are gradually replaced by nascent motor units which later become more mature.

In studying recovery of a paralyzed limb following peripheral nerve injury, one must keep in mind that supplementary movements make the limb apparently active, but these are trick motions using accessory muscles. What is apparently sensory return may be the results of ingrowth of nerves from adjacent areas, so-called overlap. In short, while a patient is apparently improving, with some restoration of function, motor and sensory, actually neither has occurred. Only trick movements have been learned, and there is regrowth of fibers for pain and temperature from adjoining areas. These new nerves have been shown to grow in at the usual rate of 1 millimeter per day.

Pain per se is not an uncommon accompaniment of a peripheral nerve lesion, but one syndrome, causalgia, is outstanding because of its severity. This interferes with the rehabilitation of the paralyzed limb, particularly in instances of lesions of the median and sciatic (tibial division). Occasionally the ulnar and peroneal nerves are affected (see Autonomic Nerve Injury).

AUTONOMIC NERVE INJURY

Involvement of the autonomic nervous system per se does not cause paralysis, but in lesions of the median and sciatic (tibial division), by adding the distressing syndrome of causalgia, the paralysis is aggravated. Treatment is interfered with. The best management of causalgia is through interrupting the sympathetic chain by repeated procaine blocks, for example, of the stellate ganglion. If lasting effects are not obtained with procaine, a preganglionic sympathectomy is done.

In Volkmann's "ischemic paralysis"[25] there is a nearly complete ischemia produced by arterial spasms of the main artery. The collateral circulation is cut off as a result of an improperly treated supracondylar fracture. While the initial care is sympathectomy, after removal of all constricting casts and dressings, the usual treatment is a procaine injection sympathectomy. If this fails, surgery must be utilized (arterectomy in toto).

CONCLUSIONS

As one reviews the nonsurgical care of traumatic paralysis in the acute, transitional and chronic stages, one cannot help being impressed by the tremendous progress that has been made, by the greater understanding of the physiology of the nervous system, the utilization of new concepts of nutrition, electrolyte balance and rehabilitation measures. Last but not least, the fuller appreciation of the psychological aspects of the patient have added to better understanding of what must be done to move the patient along a motivated, goal-directed path to recovery.

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Clinical Neuropsychology

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Medical psychology has undergone a strange and somewhat one-sided course of development during the past century, and has emerged at the present as an effort principally appropriate in most medical centers to the functions of a single discipline, namely psychiatry. The development of neuropsychology has resulted in a broadening of the base of medical psychology, making psychological methods applicable and appropriate to a wider range of medical problems. Neuropsychology refers to the area of psychological study of brain-behavior relationships from both clinical and research points of view. In this paper a brief survey of some of the clinical applications of neuropsychological knowledge will be given.

The basic assumption of clinical neuropsychology is that systematic measurement of intellectual, motor and sensory functions provides a basis from which inferences may be made regarding the organic condition of the brain. A considerable body of scientific knowledge is presently available to support this assumption,[1, 2, 3] and in the following a brief account of the application of this knowledge to clinical problems will be given.

EXAMINING PROCEDURES

In order to provide a background for understanding the rationale of the examination of the individual patient, a survey of the measures employed and the behavioral areas they cover may be helpful. The examining procedures which are administered to patients may be divided into three general categories, namely, (*a*) psychometric tests; (*b*) tests of adaptive abilities; and (*c*) tests of motor and sensory functioning.

Psychometric Tests

The Wechsler Adult Intelligence Scale is routinely administered to all adult patients. The Wechsler Intelligence Scale for Children is given to the age range for which this test is designed (CA 5-14), and the Revised Stanford-Binet is administered to younger age groups. The Wechsler Scales are administered in order to obtain an estimate of psychometric intelligence, but of equal importance is the analysis of individual subtests which permits inferences regarding lateralized as opposed to generalized encephalopathies.[4, 5, 6] While the derivation from the Wechsler-Bellevue Scales of diagnostic inferences related to specific syndromes is not a new approach, the cited references show clearly that this test has considerable utility in indicating how differential intellectual impairment relates to the hemisphere of maximal organic involvement. It has further been demonstrated that the differential patterns in the Wechsler-Bellevue Scales are related not only to the hemisphere involved, but also to the type of pathologic change underlying the particular deficits shown.[7, 8]

Tests of Adaptive Abilities

The most important measures of adaptive abilities are represented in the *Halstead Battery of Neuropsychological Tests.* The most basic way in which tests of adaptive abilities differ from tests of psychometric intelligence is that psychometric intelligence tends to an important degree to be related to specific educational and experiential background factors, while the tests of adaptive abilities are carefully designed to minimize such variables, and to give an estimate of the patient's ability to respond to an immediate problem-solving task which is only minimally dependent upon previously acquired information. While these tests have been described in detail by Halstead,[1] a short description of the tests will be given here. The *Category Test* is a multiple choice, abstraction test presented with a projection apparatus. Except for the instructions, the test is nonverbal and the patient responds by selecting one of four keys for the correct answer. The *Tactual Performance Test* is a measure of complex psychomotor ability with the successful completion of the task depending upon the use of motor, tactile and kinesthetic functions without the benefit of visual clues. In addition to giving an indication of general level of adaptive abilities, this test is also helpful in determining lateralization of a lesion since test trials are given independently to each hand, and differential relationships in performance between the hands may be obtained depending upon the type and location of the involvement. The *Rhythm Test* is administered to measure the patient's ability to sustain auditory attention in a sound discrimination task. The *Speech Perception Test* gives an estimate of ability to perceive and to discriminate among speech sounds. The *Finger Tapping Test* provides a quantitative measure of the patient's finger oscillation rate. Both hands are examined individually, and important deviations from the normal relationship between the dominant and nondominant hand represent one of several bases for making inferences regarding possible lateralization of a lesion. The Finger Tapping Test, when evaluated in conjunction with the Tactual Performance Test, has also been shown to be of considerable value in localizing a lesion on the anteroposterior axis in the dysfunctional hemisphere.

In addition to the tests from the Halstead Battery just described, the *Trail Making Test* is administered. This test, which is further described in the references, has been shown to have a high degree of ability to discriminate between groups with and without brain damage. This test has also proved helpful in determining the hemisphere of maximal involvement.[9] The *Aphasia Test* used as part of the examining procedure is a modification of the Halstead-Wepman Test.[10] This test surveys expressive and receptive language functions related to both verbal and written language, and also includes a number of items designed to reveal apractognostic symptoms. The general validity of the Aphasia Test to the problems of organic brain function has been demonstrated in numerous studies.[5, 11]

Tests of Motor and Sensory Functions

A number of tests of motor and sensory functions are routinely administered. The Finger Tapping Test was previously described. As an additional aspect of evaluation of motor functioning, a *Motor Steadiness Battery* is included. This battery of tests includes quantitative assessment of static and kinetic tremor and fine manipulative speed and coordination. These measures are also given independently for the two hands and may provide a basis for inferences regarding lateralization based upon differential relationships between performance on the dominant and nondominant hands, and for differential diagnosis in the relationship between static and kinetic tremor.

The sensory examination includes standardized quantifiable procedures for assessing finger gnosia, fingertip number writing perception, tactile form recognition, and sandpaper roughness discrimination. Examination for tactile, auditory and visual imperception under conditions of bilateral simultaneous stimulation is also part of the sensory examination. Because evaluation and interpretation of our test results depend heavily upon establishment of hand and hemisphere dominance, a survey of hand, foot and eye dominance is performed in a standard and systematic fashion. All tests administered as part of the neuropsychological battery are administered in a uniform fashion from patient to patient, and each individual response is recorded quantitatively, providing an opportunity to compare results in successive examinations.

While the test battery which has been described above is used with adult patients, modifications of this battery for subjects 9 through 14 years of age and for subjects in the kindergarten and primary grades have also been developed, and considerable normative and clinical data have been collected.[12, 13]

CONTRIBUTIONS OF THE METHODOLOGICAL APPROACH TO DIAGNOSIS

There are several basic methodologies that may be applied in the psychological evaluation of neurological patients. However, the methods described here are those which have been subject to thorough scientific evaluation with respect to validity and general pertinence to the problem of brain-behavior relationships. The neuropsychological evaluation of clinical problems in neurology is particularly pertinent in two major areas. The one area is in diagnosis of presence or absence of encephalopathy including differential diagnosis, and the other area is represented by those instances in which the diagnosis has been well established, but where an evaluation of the intellectual and adaptive consequences of the lesion (e.g., post-traumatic conditions) is essential.

The traditional diagnostic contribution of clinical psychology to clinical neurology has been limited to inferences that a particular patient does or does not show signs of "organicity." While many of the methods used in clinical psychology for identification of brain lesions have considerable validity, it is interesting to observe that most of these tests are particularly pertinent to the problem of assessing intellectual functions associated with the right (minor) hemisphere. Tests of this kind are represented by the Block Design subtest of the Wechsler-Bellevue Scale and various tests of spatial orientation. Tests of the left (major) hemisphere, which are mainly tests of symbolic and verbal functions, have been considerably less used because these tests tend to measure psychometric intelligence as well as any specific defect associated with encephalopathy, and because of widely held opinions that tests of this kind are relatively resistant to the effects of brain injury.

While the psychological evaluation of neurological cases until recently has been limited to the question of presence or absence of brain damage, the contribution of neuropsychology has changed this approach, and the questions that the clinical neuropsychological evaluation of patients attempts to answer are similar to those of clinical neurology; only the methodological approach is different. The following are some of the questions that may be successfully answered on the basis of neuropsychological data. Is there evidence of encephalopathy? If so, is there evidence of a lateralized lesion, or is the condition generalized, involving both hemispheres? If generalized, what is the pathology? Is it vascular disease or neurogenic degeneration? If the pattern of test results is indicative of lateralized brain disease, what lobe or area is maximally involved? Again the question of type of pathologic change must be evaluated and the full range of possible conditions from neoplastic and vascular involvement to degenerative, demyelinating and traumatic lesions must be considered. In case of possible neoplastic disease, an evaluation as to whether it is an intrinsic or extrinsic tumor must be made.

APPLICATIONS IN DIFFERENTIAL DIAGNOSIS

In the following, a few comments will be made with respect to the neuropsychological characteristics of some of the more common neurological syndromes and diseases. This is not meant to be a complete account either of our present knowledge concerning neuropsychological inferences regarding cerebral disease, or of the range and variability of these characteristics in individual patients. Rather, it represents an attempt to give a brief survey of the average constellation of the intellectual and motor-sensory status in the conditions described. When in the following the term "behavior" is used, it refers to the area of intellectual and motor-sensory functions rather than to personality traits and affective status.

Cerebral Neoplasms

The behavioral effects of neoplastic brain disease appear to be related to two main factors, namely, pathology and lateralization. The effects of extrinsic tumors, notably meningiomas, are almost without exception significantly less severe than those associated with primary or infiltrating tumors. Once a meningioma reaches a size sufficient to give objective clinical symptoms, a mild to moderate degree of impairment of adaptive abilities is evident, while measurable decline or selective impairment of psychometric intelligence is rarely observed. On the Wechsler-Bellevue Scale these patients will obtain a psychometric level commensurate with their education and occupation without any conspicuous discrepancy between verbal-symbolic abilities on the one hand, and spatial and temporal abilities on the other hand, even when such lesions give rise to mild dysphasia. However, in tests requiring immediate problem solving ability and adaptation to new learning situations (e.g., Category Test) there usually is a moderate, but measurable, deficiency compared to the relatively unimpaired psychometric intelligence level. Since meningiomas tend to occur in middle age or later, a general aging effect is a complicating factor which at times may be identical to the effects of extrinsic tumors. This usually does not represent a differential diagnostic problem, however, because the pattern of motor and sensory impairment found with extrinsic tumors seems to give considerable help in this type of differentiation. In extrinsic, space-occupying lesions, there is usually a mild but consistent impairment of sensory, motor (Tapping and Dynamometer) and psychomotor (Tactual Performance Test) functions if the lesion is in the temporoparietal-occipital area. However, with frontal location the sensory and psychomotor pattern tends to be normal while the simple motor tests show fairly definite impairment. With anterior frontal location the neuropsychological identification of a lesion may at times be impossible, both in terms of motor-sensory and intellectual deficits. In general, all findings tend to be quite mild, but vary with the size of the lesion. One exception to this picture, however, is represented by parasagittal meningioma. In these cases we usually find much more pronounced deficits, mainly in adaptive abilities and to a lesser extent also in psychometric intelligence. The psychometric intelligence pattern will also, in these cases, often fail to show significant differential impairment.

Although it is often difficult positively to identify a meningioma on the basis of neuropsychological data, the effects of these lesions are dramatically different from those caused by infiltrating brain tumors.

The effects of destructive, rapidly progressive neoplasms on behavior are generally quite dramatic. In gliomatous lesions a readily identifiable differential impairment of psychometric intelligence, depending upon the hemisphere of involvement, is usually present. With intrinsic lesions in the left (major) hemisphere, there is a marked decline in verbal subtests as compared with performance subtests on the Wechsler-Bellevue Scale. This is generally the case even in the absence of clinical dysphasia.

Conversely, with lesions of the right (minor) hemisphere, a pronounced deficit is found in performance-type abilities (spatial and sequential abilities). Deficits in adaptive abilities are very pronounced. On tests requiring sustained attention (Rhythm Test and Speech Perception Test), severe deficits are almost always present while these tests usually give normal or near normal results in lateralized meningiomata. Even in the absence of reflexological changes, evidence of lateralized impairment in the neuropsychological test pattern is the rule in infiltrating neoplasms. Simple motor functions (Finger Tapping Test), more complex psychomotor functions (Tactual Performance Test), and motor steadiness and coordination (Motor Steadiness Battery) are usually impaired on the side contralateral to the lesion. One characteristic finding in tumor cases as opposed to cases with cerebrovascular accidents is that motor functions on the body side homolateral to the lesion usually are quite normal, while in vascular disease the motor performance generally is impaired bilaterally, but with the motor function contralateral to the cerebrovascular accident usually even more impaired than in tumor cases. The pattern of motor impairment in tumor cases is related to location of the maximal area of involvement on the posteroanterior axis. With maximal structural involvement in the frontal area, simple motor functions (Finger Tapping Test) are relatively more impaired than are psychomotor functions. As the area of maximal involvement is moved posteriorly, there is a decline in psychomotor ability and often relatively less impairment of simple motor functions.

In addition to the conventional parietal lobe signs, sensory imperception under conditions of bilateral simultaneous stimulation is usually found with infiltrating lesions, and this phenomenon seems to occur more often in association with lesions of the right (minor) hemisphere than the left (major) hemisphere.[14] While visual field defects often are found in neoplasms of the posterior parts of the hemispheres, visual imperception usually may be identified prior to the development of visual field defects or may be present in patients in whom field defects never are demonstrated.

In addition to having lateralized significance, the presence of tactile, auditory and visual imperception should be viewed as a sign of structural involvement and intellectual deterioration.[15]

In summary, the behavioral defects associated with lateralized infiltrating neoplasms are characterized by differential intellectual impairment related to the hemisphere of involvement. In addition, there is a pronounced defect in adaptive abilities (abstraction, attention, sensory discrimination). Indications of lateralized motor impairment are almost always found, even in cases with normal neurological status.[3] Lateralized sensory imperception is frequently demonstrated in these cases.

In patients with infiltrating neoplasms of relatively slow development (e.g., oligodendroglioma) the differential impairment of psychometric intelligence may not be present. Patients with extensive involvement of the left (major) hemisphere may not demonstrate clinical dysphasia, and patients with corresponding involvement of the right (minor) hemisphere may not show the rather profound apractognostic symptoms seen with rapidly developing lesions. It is therefore somewhat surprising to find that, while the specific intellectual defects associated with the one or other hemisphere may be quite mild in association with slowly developing infiltrating neoplasms, the general impairment of adaptive abilities, psychomotor and sensory functions is usually almost as profound and severe as in patients with rapidly progressive lesions.

Cerebrovascular Disease

The outstanding neuropsychological characteristics of patients with cerebrovascular disease, but without major cerebrovascular accidents, is a general impairment of adaptive abilities, and a pattern on the Wechsler-Bellevue Scale which shows a considerable variability between subtests, indicating a decline in certain areas (Digit Span, Digit Symbols Subtests in particular) while other subtests may be on a much higher level (Information and Vocabulary are examples of these types of abilities). Tests of ability to sustain attention and auditory discrimination are invariably impaired in advanced cases, while these abilities may be near normal in early stages of the disease. In motor function, these patients' most characteristic feature is bilateral slowness and an increase in both static and kinetic tremor, as measured by the Motor Steadiness Battery. Sensory impairment, particularly finger dysgnosia and impairment of fingertip number writing perception, is a quite stable finding in association with the general intellectual impairment in these patients. Usually the impairment of adaptive abilities (difficulty with abstraction and new problem solving situations) is much more pronounced than one would suspect from casual contact with these patients.

When the cerebrovascular disease is associated with a cerebrovascular accident of sufficient size to be clinically recognized, the lateralizing findings which were described under rapidly developing cerebral neoplasms will be present. The main differential characteristic between lateralized infiltrating lesions and strokes is that the tumor patient's symptoms tend to be much more unilateral than the stroke patient's. The cerebrovascular disease process, which presumably brought on the stroke, is a diffuse process involving both hemispheres.

Multiple Sclerosis

While the clinical symptomatology in multiple sclerosis often is characterized by inconsistency and variability, the early and typical neuropsychological picture is surprisingly stable. The usual finding is a pattern characterized by normal or essentially normal intellectual functions, but varying degree of motor impairment. In other words, there is an unusual dissociation of intellectual and motor functions. The sensory pattern is more unpredictable, but the functions that are examined as a part of our test battery are usually normal.

In more advanced cases, intellectual and sensory defects become a rather predictable part of the picture, and while the motor functions to a certain extent will improve during remissions there is as a rule no great improvement in intellectual functions during remissions. A survey of a large number of serially examined patients, some of whom had been followed up to seven years, gives the over-all impression of a slow but steady decline in intellectual functions, often unrelated to the changes in motor status. Cases have been found in which marked intellectual impairment is present very early in the development of the disease, but these instances are quite rare.

Closed Head Injury

These patients typically present a picture of bilateral involvement which includes both psychometric and adaptive abilities, and motor and sensory functions. The involvement of function in both cerebral hemispheres is probably the most stable finding in these patients. The diagnostic aspect of this condition, once subdural hematoma is ruled out, is typically one of evaluation of the general behavioral effects of the trauma. Our impression at the present is that significant improvement in severe cases takes place for at least 12 months and possibly as long as 18 months. However, if no improvement has taken place during a period of three to four months within any period of the first 12 months, little further improvement may be expected. In one study[3] three groups of subjects were compared, including a non-neurologic control group, a group of brain-injured patients with positive findings on the physical neurological examination, and a brain-damaged group with negative physical neurological status. The two neurological groups were matched for type of lesions. On the psychological measures no differences were found between the "positive" and "negative" neurological groups, but both of these groups were significantly different from the control group on all the measures except one. Although this study has several implications, one interesting conclusion is that no positive relationship exists between the physical neurological status and the level of intellectual functioning. These findings would seem to have considerable significance for evaluation of the post-traumatic syndrome, and traumatic conditions represent an area of special pertinence for neuropsychological evaluation.

CASE REPORT

For the purpose of demonstration, one case report is presented. It is hoped that this may contribute to a better understanding of the approach and procedures of neuropsychology.

The patient was examined in a standard fashion. The tests were all administered and scored by experienced technicians, and the report was written on the basis of an interpretation of the test scores and knowledge of the patient's sex, education and age only. Knowledge of the patient's symptoms or clinical findings was not available when the report was written.

J.B., age 20, female, education 11. Date of testing 10/16/58

WECHSLER-BELLEVUE (FORM I)		HALSTEAD BATTERY	
Verbal IQ	91	Category Test	45
Performance IQ	76	Flicker Cps (not given)	
Full Scale IQ	82	Flicker Deviation (not given)	
Verbal Weighted Score	40	Tactual Performance Test	
Performance Weighted Score	33	Total Time	26.3
Total Weighted Score	73	1. Left Hand*	11.8
Information	8	2. Left Hand	4.7
Comprehension	10	3. Both Hands	9.8
Digit Span	7	Memory	2
Arithmetic	4	Location	1
Similarities	11	Seashore Rhythm Test	5
Vocabulary	9	Speech Perception Test	8
Picture Arrangement	4	Finger Tapping	
Picture Completion	12	Right Hand	13
Block Design	6	Left Hand	33
Object Assembly	7	Time Sense	
Digit Symbol	4	Memory	317.3
Trail Making Test		Visual	315.6
A	93″	Impairment Index	.8
B	125″		
Total	218″		

* Could not perform task with right hand.

APHASIC SYMPTOMS (Modified Halstead-Wepman Aphasia Screening Test): Possible mild dyslexia, mild dyscalculia and mild enunciatory dyspraxia.

SENSORY IMPERCEPTION. *Tactile:* Hypesthesia right face. Hands normal on single stimulation, but consistent imperception of the stimuli to the right hand under conditions of bilateral simultaneous stimulation of right hand and left hand, and right hand and left face.

Auditory: Normal finding with unilateral auditory stimulation, but consistent imperception of auditory stimuli on the right side under conditions of bilateral simultaneous stimulation.

Visual: Right homonymous field deficit, examination for sensory imperception not carried out.

FINGER GNOSIA. Right hand: Eleven errors in twenty trials. Left hand: Three errors in twenty trials.

PERCEPTION OF FINGERTIP NUMBER WRITING. Right hand: Ten errors in twenty trials. Left hand: One error in twenty trials.

STEREOGNOSIS. Right hand: Five errors in six trials. Left hand: One error in six trials.

APRACTOGNOSTIC SYMPTOMS. Slight impairment in copying of simple geometric figures, but this was judged to be more related to incoordination and tremor than to real spatial distortion.

NEUROPSYCHOLOGICAL REPORT. Tests of Biological Intelligence yielded an Impairment Index of .8, indicating moderate impairment of abilities dependent upon organic brain function. Analysis of the pattern of test results consistently points toward a rather severely dysfunctional left hemisphere. The patient was not able to perform the Tactual Performance Test with the right hand, and the scores on the Finger Tapping Test were right hand 13, left hand 33. Aphasia examination revealed the following symptoms: very mild dyslexia, mild enunciatory dyspraxia, and mild dyscalculia. Examination for tactile imperception showed a tendency to suppress tactile stimuli to the right in the following combinations: left hand–right hand, and right hand–left face. Examination for auditory imperception showed a strong tendency to suppress stimuli to the right ear when both ears were stimulated simultaneously. Examination for visual imperception was not performed since a right homonymous hemianopia was revealed. Finger agnosia was present on the right hand, and fingertip number writing was also more impaired for the right hand than the left hand. Examination of stereognosis showed pronounced defects of the right hand as compared to the left hand. The patient's ability to copy geometric figures was slightly impaired, but it is felt that this related more to incoordination and tremor of the left hand than a real spatial distortion. The patient had definite difficulties in holding a pencil in the right hand. It is also felt that her somewhat cluttered writing is due to the motor deficiency in the right hand.

The Category Test gave a score of 45, which is fairly close to being normal for a person with this educational background. Part B of the Trail Making Test was performed in 125 seconds. The Wechsler-Bellevue Verbal Weighted Score is 40, the Performance Weighted Score 33. The subtest pattern shows very deficient performance on Picture Arrangement suggesting an area of dysfunction in the right temporal lobe. However, there are no other definite findings to support a lesion in this area. Speech perception gave a score of 8, which is just one mistake more than the mean of a normal control group.

COMMENT. The pattern of test results obtained on this patient is quite consistent with some type of destructive lesion in the posterior part of the left hemisphere. The unusual feature in the test pattern is that there are only very mild signs of aphasia, and this together with fairly good performance on both the Category and the Trails tests would strongly indicate that the lesion is a relatively slowly developing one. In reviewing patients with similar patterns in the past, we have found that these patients have had slow-growing neoplastic lesions, like oligodendroglioma or ependymoma. It appears that the area of involvement in this patient is relatively large, and the possibility of metastatic lesions is very unlikely. Although we feel strongly that this patient has an intrinsic tumor, it is from our experience very unlikely that it is a glioblastoma multiforme. Our best inference would be an astrocytoma, ependymoma or also possibly an oligodendroglioma. The area of maximum involvement appears to be the superior part of the parietal lobe, extending from the superior part of the central sulcus posteriorly into the occipital lobe and down into the inferior posterior part of the temporal lobe. Judging from the lack of very strong aphasic symptoms, the inferior posterior part of the frontal lobe and the area immediately around the sylvian fissure should be less involved than the areas just mentioned.

Neurological Summary

Present Illness: Patient had episodes of numbness in her right arm since her last year in high school. In the past year her right arm has become increasingly numb, and she has developed a mild right hemiparesis and severe headaches.

Examination: Somewhat slow in mentation; right homonymous hemianopsia; marked swelling of right face from abscessed tooth; right hemihypesthesia; right hemiparesis; figure writing and stereognosis, poor right; reflexes more active right.

Diagnostic Studies: EEG—Delta Grade II, left frontoparietal. X-rays—skull: demineralization of posterior clinoids; carotid arteriogram: left posterior parietal mass, marked shift left to right.

Diagnosis: Ependymoma—left occipitoparietal area.

Comments on the Neuropsychological Report

The neuropsychological findings in this patient are quite typical of a structural involvement of the posterior part of the left cerebral hemisphere. However, the two following findings relating to symbolic and verbal functioning were unusual. The aphasia examination yielded almost normal findings, and the Verbal Weighted Score was higher than the Performance Weighted Score on the Wechsler-Bellevue Test. In the context of the over-all test pattern, this observation was of crucial importance for making inferences regarding the type of pathology responsible for the rather obvious involvement of the left hemisphere. We have repeatedly found that slowly developing neoplasms may fail to produce specific defects in psychometric abilities and symbolic language functions, while the over-all impairment of adaptive abilities often is almost as pronounced as in cases with rapidly developing infiltrating lesions.

A final point to be made is that the neuropsychological inferences to a large extent were made on the basis of the constellation of the patient's intellectual pattern. This represents an area of evidence which is clearly in the domain of the so-called "higher mental functions," and thus represents a source of information not systematically utilized in clinical neurology.

The objective of this article has been to familiarize the reader with some of the methodological approaches and findings of contemporary neuropsychology. It was not intended as a survey of neuropsychology, but rather as an attempt to indicate new problem areas where psychological methods may be pertinent.

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Clinical Diagnostic Tests for Brain Tumors

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THE DIAGNOSIS of a brain tumor is more readily established if the clinician has a high index of suspicion for this entity. Many of the methods available for establishing a diagnosis are outgrowths of the neurological examination. The use of these special methods depends in large part on the clues provided by the patient's history as well as on the findings on the conventional, complete neurological examination. Emphasis on detailed evaluation of the optic pathways, hearing and vestibular functions and mental status depends upon the previously elicited findings. Other clinical tests are laboratory studies in the more conventional sense of the word, and depend upon special examination of body fluids or evaluation of the electrical activity of the brain or the use of radiologic techniques.

In discussing the clinical tests which may be employed in a given case an effort will be made to consider them in an order of increasing complexity, the simplest measures being mentioned first.

EXAMINATION OF BLOOD AND SPINAL FLUID

Primary tumors of the brain usually produce no abnormalities in body fluids other than the cerebrospinal fluid (CSF). Metastatic tumors, of course, produce findings depending upon their site of origin or other organs which have been invaded. One report[8] indicates the presence of elevated sedimentation rates in a majority of patients showing glioblastoma multiforme, but this would seem to be the only exception to the rule that primary brain tumors cause no changes in the hemogram or blood chemistry studies.

Cerebrospinal fluid abnormalities are present in a large percentage of patients with intracranial tumors.[6, 12] The clinician must be aware, however, that a lumbar puncture should not be performed when the diagnosis is already obvious, particularly when there is clinical or x-ray evidence of increased intracranial pressure. In such cases the clinician must be prepared to have the patient placed in a situation where complete vigilance can be maintained in the event that increased intracranial pressure is confirmed at the time of the lumbar puncture. Once changes in the patient's state of conciousness, variations in the neurological findings or abnormalities of the patient's vital signs begin to occur, definitive diagnosis and surgical intervention may be a matter of great urgency.

When the diagnosis of an intracranial mass is not obvious and the lumbar puncture is performed, the most important findings will consist of measurement of the patient's CSF pressure in the lateral recumbent position with the needle in the lumbar subarachnoid space, observation of the color of the cerebrospinal fluid, and the measurement of the protein content of the fluid.

With the needle in the lumbar subarachnoid space and the patient in the lateral recumbent position a value of 200 millimeters of spinal fluid or above is considered to be a reflection of increased intracranial pressure. In order to avoid false elevations the operator should take pains to have the patient relaxed with legs and body in a normally extended position. It is desirable to wait for five minutes by the clock to insure that equilibrium has been attained and that the pressure reading is an accurate one. On most occasions small fluctuations in the meniscus of the spinal fluid within the manometer may be observed which reflect pulsations of the arterial system. Compression of the jugular veins or other compression of the neck is contraindicated in all instances of intracranial lesions of any sort. Such a maneuver cannot provide any useful information to the operator in terms of the nature or the site of the lesion. Herniation of the contents of the various compartments of the skull producing a life-life-threatening situation may result.

The cerebrospinal fluid is normally tap-water clear. To insure that this observation is accurate the operator should hold a specimen tube to the daylight or against a white background and compare it with an adjacent tube filled with tap water. Any haziness or tendency for yellowish discoloration (xanthochromia) represents an abnormality. High protein content of the fluid may produce moderate degrees of xanthochromia. The presence of a total protein content of more than 50 mg. per 100 ml. is considered abnormal.

In patients with intracranial tumors the cell count of cerebrospinal fluid is usually normal. There may be, however, elevation of the white cell series to a value greater than 5 per cubic millimeter with highly malignant tumors. With invasion of the meninges the cell count may reach a level of 100 or more. Malignant cells may also be noted with the use of appropriate techniques, which usually involve spinning the cells down and making an examination of the cell block with appropriate stains.[11, 20]

The sugar content of cerebrospinal fluid is usually normal in the presence of brain tumors unless there has been an invasion of the meninges and a cellular response.

Enzyme activity has been measured in cerebrospinal fluid for several enzymes.[19, 21] These studies have shown that although there may be elevation of the enzyme activities, it is usually a reflection of increased protein content, the presence of young cells or an alteration of the blood-CSF barrier. The application of refined enzyme activity measurements, particularly the use of isoenzyme activity changes, has not been fully evaluated.

In summary, the most useful cerebrospinal fluid findings to the clinician in confirming the presence of a brain tumor are increased pressure and elevation of CSF protein. The hazards of lumbar puncture in the presence of brain tumor are emphasized.

NEURO-OPHTHALMOLOGY

This topic and the two following it emphasize the extension of the neurological examination through other disciplines. Some of the techniques employed are not properly thought of as tests but represent a discriminative clinical examination.

A general effect of brain tumors, when increased intracranial pressure is present, is edema of the optic disc. Frank papilledema is not difficult to recognize. There are early stages, however, which become very difficult to interpret. Mild elevation of disc margins, some rolling of the arterioles and venules, absence of cupping, and some dilatation of venules may not necessarily indicate increased intracranial pressure or papilledema. In such situations visual field testing may be helpful. The earliest change may be just enough edema to produce enlargement of the normal blind spot. This may best be demonstrated by plotting the blind spot at 1 meter with a 5 millimeter object.

Localized damage to parts of the nervous system may give rise to other types of visual field defects. A lesion pressing on the optic nerve rostral to the chiasm will produce general depression of visual acuity and some pallor of the optic nerve head as seen on funduscopic examination and ultimately may lead to unilateral blindness. Lesions caudal to the chiasm will produce symptoms referable to the optic tract, and the characteristic feature here is homonymous hemianopsia. Discrete lesions of the temporal lobe will produce quadrant defects (superior quadrantanopsia). Discrete lesions of the occipital lobe may produce quadrant or sector defects. An important visual defect seen with pituitary tumors or other lesions of the chiasm is bitemporal hemianopsia.

Brain tumors may cause disturbances of ocular motility. The sixth nerve (abducens), because of its long intracranial course, may be compressed from increased intracranial pressure and there may be a lateral rectus palsy as a false localizing sign. Incisural herniations often compress the oculomotor nerve, producing oculomotor palsies.

NEURO-OTOLOGY

Examination of auditory and vestibular functions may be of help in the diagnosis of brain tumors. Acoustic neurinomas practically always produce hearing loss. The vestibular function is also absent in a high percentage of the cases and this can be demonstrated by stimulating the labyrinth (caloric testing) by means of the instillation of ice cold water into the external meatus.[15]

Recent studies[17] suggest that alteration of sound localization may occur in patients with lesions of the temporal lobe. Quantitative measurement of this type of deficit is not widely available, but the lack of sound localization may sometimes be demonstrated at the bedside with the patient blindfolded and having him try to identify the point in space from which a standard sound stimulus is delivered.

NEUROPSYCHOLOGY

Psychological testing in patients with brain tumors may show deficits of a generalized nature suggesting encephalopathy (dementia), or the testing may reveal specific deficits which help to provide localization for certain subdivisions of supratentorial and infratentorial structures. The usual psychological testing is designed to answer questions about intelligence, about cognitive deficits or decline in mental efficiency, about aptitudes and interests, and about personality. In order to pursue these four categories of tests the subject must be alert and cooperative enough so that some satisfactory minimum performance is achieved. If the patient's performance is obviously below the normal range, many questions of localization of lesions will still remain.

In an effort to provide greater evidence for localization of lesions, different types of tests (neuropsychological testing) have been developed which are designed to elicit deficits of each of the lobes of the hemispheres. Thus, the patient is asked to perform tasks which will bring out deficits of dominant frontal, nondominant frontal, dominant parietal, nondominant parietal, dominant temporal, nondominant temporal and finally dominant occipital and nondominant occipital lobes. The success of this type of testing in localization of certain types of tumors has been notable.[7, 16] As further studies in this type of testing are pursued, information may also be obtained which will be helpful in localizing lesions of the extrapyramidal and cerebellar systems.

ELECTROENCEPHALOGRAPHY

Measurement of the patient's brain waves (electroencephalography) may be of great help in establishing the diagnosis of a brain tumor located in the cerebral hemispheres.[1] Changes in brain wave activity in tumors of the posterior fossa occur but the interpretation of these is more difficult.[4]

The normal brain wave activity consists of wave patterns at a frequency of 8 to 12 per second. The presence of slow focal patterns in the area of the cerebral neoplasm is the most helpful finding for localization on EEG. There is nothing specific about slow focal patterns since they may occur around areas of infection, hemorrhage or inflammation. Thus the history and other neurological findings become crucial in interpretation of EEG abnormalities. The slow wave abnormality is produced from cerebral tissue along the margins of the neoplasm, the neoplasm itself being electrically silent. Estimations of the size of the tumor on the basis of EEG findings are not reliable since the electrical changes are dependent upon various other factors such as the amount of edema surrounding the tumor and the presence of ischemia or other nutritional changes in the neighborhood of the tumor.

One negative tracing is inadequate if there is a strong clinical suspicion of a brain tumor. With the evolution of the patient's signs, the likelihood of finding EEG abnormalities on serial tracings on patients with tumors above the tentorium is good.[9]

NEURORADIOLOGY

Neurologists and neurosurgeons could not function as modern clinicians without present-day roentgen examinations.[5, 13, 14] The sound clinician is obligated to weigh the risk of the procedure against the potential reward of learning the nature of the patient's problem. Some radiological examinations are uncomfortable and may increase pre-existing deficits. Occasionally, serious complications ensue. It should be emphasized that roentgenograms of other areas of the body may be extremely important in interpreting neurological syndromes. The physician can ill afford, for example, to overlook the fact that a high percentage of metastatic tumors and primary lung tumors can be demonstrated, at some point in the patient's course, on roentgen examination of the chest. In the following sections plain skull films, ventriculography, pneumoencephalography and angiography will be discussed.

Plain Skull Films

Plain skull films are a valuable and readily available form of examination. Films of this sort may show increased intracranial pressure. In children, increased pressure may be demonstrated by a widening of the cranial sutures, which may amount to several millimeters and even a few centimeters. It is a reliable sign but rarely found after the age of 14 years.

A second finding which may indicate the presence of increased intracranial pressure is decalcification of the sella turcica and erosion of the posterior clinoid processes. This sign is best seen in patients in whom there has been an insidious increase in intracranial pressure over a period of several weeks to a few months. The exact time needed for the development of this radiological sign is not known. It is postulated that with the development of an internal hydrocephalus the ventricular system, including the third ventricle, causes a downward pressure upon the sella and an erosion of the posterior clinoid processes and the dorsum of the sella. In older patients or in patients in whom there has been demineralization of the bones due to metabolic disease, an interpretation of increased pressure simply on the basis of demineralization of the structures in the region of the sella is not justified. The presence of these changes, however, in a patient with appropriate neurological signs (personality change, decreased level of awareness, drowsiness, and so on) may be helpful as an indication of serious intracranial disease. Pituitary tumors may also cause alterations in the size and shape of the sella turcica. These changes are due to direct pressure within the sella rather than to pressure at a distance. The normal measurements of the sella are 8 to 12 millimeters in the anteroposterior diameter and 6 to 8 millimeters in depth. The shape may vary considerably. The reader is referred to textbooks and monographs of radiology for detailed descriptions of the variations.

Another sign which may indicate increased intracranial pressure is an increase in the convolutional impressions, which is sometimes called the "beaten silver" sign. This is more often present in childhood than in later life. It is not in itself sufficient to make the diagnosis of increased intracranial pressure and the physician should be aware of the fact that adults may have impressive intracranial hypertension without showing this roentgen sign.

Another valuable sign on plain film examination of the skull is the displacement of certain structures. If calcifications are present and they are displaced from the expected position, the physician should be immediately alerted to the presence of a mass. Displacement of the calcified pineal gland is a very important indication of intracranial disease. Shifts of the pineal of more than 3 millimeters as viewed in the frontal projection should be regarded as strongly suspicious for intracranial disease. Occasionally the pineal will be shifted in two planes, laterally from the midline and in one other direction. Alteration in the midline position as viewed from the frontal projection, however, is the most reliable and easy to interpret form of pineal shift. Shift of the pineal gland may be due to pressure of a tumor forcing the gland to the opposite side of the skull or may be due to traction from an atrophic lesion pulling the gland toward the area of atrophy.

Calcification of tumors may occur. If this is present in the plain films, the importance is obvious. The most commonly calcifying tumors are meningiomas, craniopharyngiomas and oligodendrogliomas. Calcification may also be seen in astrocytomas and ependymomas. A special form of bony response may occur in the presence of meningiomas. Meningiomas tend to invoke a hyperostotic response in the bones adjacent to them. If this occurs along an inner table of the calvarium and extends through the outer table, the patient's skull may show an external swelling. Roentgen examination will show an increased density in the area in which this response is present. Meningiomas may also show a mixture of bone destruction and proliferation. Osteolytic lesions which have a sharply punched out appearance, however, are not characteristic of meningiomas and should alert the examiner to the presence of a metastic lesion or other systemic diseases such as multiple myeloma. Occasionally meningiomas may be suspected from plain skull examination by an associated increased vascularity of the skull. Meningiomas are frequently very vascular tumors. Reflection of this may be seen bỳ a widened groove of the middle meningeal artery especially in convexity meningiomas.

Pneumoencephalography and Ventriculography

Twenty-five years ago it was said that plain films of the skull would show changes reflecting either increased pressure or some other abnormality which would give clues to the histological type of the tumor in 75 per cent of the cases. It is recognized that this figure is not applicable at the present time because of the earlier stages of disease at which most patients are studies. At the present time approximately 20 per cent of the patients present localizing findings and an additional 20 per cent may show signs of increased pressure as noted in the plain film of the skull. By the use of major radiological procedures, such as ventriculography, pneumoencephalography and arteriography, it is possible to confirm diagnoses of intracranial tumors in as high as 90 per cent of the cases examined.[5]

PNEUMOENCEPHALOGRAPHY. Almost all clinics are in agreement that pneumoencephalography in the presence of intracranial masses may be a hazardous procedure. Some clinics almost categorically refuse to do pneumoencephalography as the initial procedure, preferring to have trephine openings previously made by the neurosurgeon. Other clinics emphasize the safety of pneumoencephalography if the procedure is performed in the morning of a given day with operating room time available following the air study if a tumor is found. The essence of the regimen is that no undue length of time elapse between the time of the pneumoencephalogram and the craniotomy. Frequently, tumors of the posterior fossa which distort the basal cisterns and tumors in the fourth ventricle, as well as some tumors of the third ventricle, can be satisfactorily demonstrated only in this way since gas injected via the lateral ventricles usually does not provide adequate visualization of the posterior fossa structures and the basal cisterns (Fig. 1).

The technique for pneumoencephalography is relatively simple. Some

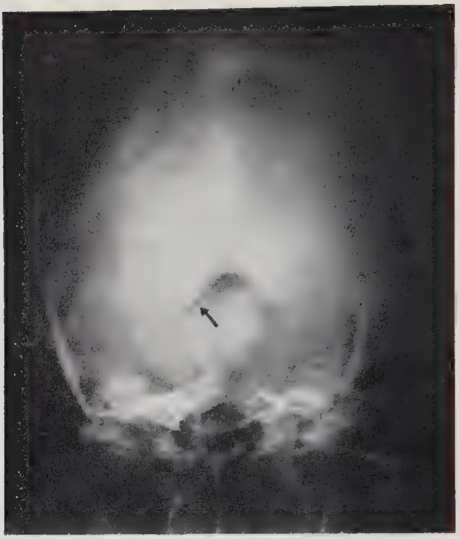


Fig. 1. Towne projection of a pneumoencephalogram showing gas in the fourth ventricle. The arrow indicates the border of a convex mass (ependymoma) which projects into the ventricle. (Courtesy of Dr. John H. Juhl.)

clinics prefer to remove fairly large amounts of spinal fluid (60 to 100 cc.), replacing it with a gas. The gas which has the widest preference is room air. Occasionally oxygen or other gases may be used. The technique in these larger volume air studies consists of removing a slightly larger volume of spinal fluid than is replaced by room air. Thus the patient may have 20 cc. of CSF removed, 10 cc. of air instilled, 10 cc. of CSF removed, 10 more cc. of room air instilled, and so on, until the desired amount is obtained.

In recent years the technique of fractional pneumoencephalography has become accepted. This procedure involves removal of only enough CSF to make necessary laboratory studies on the fluid and then the injection of air into the subarachnoid space. After the first 10 cc. of air is slowly injected, a check film is made in the lateral and posteroanterior positions. If the air is observed in the ventricular system an additional 10 to 20 cc. is injected and the needle is withdrawn. However, if more air is necessary, additional amounts are injected and additional check films are taken. The essence of the fractional pneumoencephalogram is the use of smaller amounts of gas and the removal of very little cerebral spinal fluid.

Whether the larger or the fractional pneumogram is done, the position of the patient is, of course, the same. The patient is seated in an upright position with his back to the operator and the head flexed 30 to 45 degrees. After the first aliquot of gas is instilled, a check film is taken which reveals many of the posterior fossa structures. This first film is sometimes called the Robertson view.

Intracranial masses can be localized on pneumograms by one or more types of abnormalities. The most common sign is a displacement of the ventricular system due to pressure of the mass itself. A second type of sign is the direct visualization of the tumor mass within the ventricular cavity with air partly surrounding the tumor. A third but rare sign may be the presence of air within a cyst in the tumor. Lastly, tumors may produce obstruction and thus cause nonfilling of the ventricles when the gas is injected from below. Figures 1 and 2 show the impressive distortion which may occur in the posterior fossa structures when a tumor is present in the fourth ventricle. In this case the tumor was an ependymoma, which may be seen as a convex mass outlined by the gas in the fourth ventricle. Lateral projection reveals an internal hydrocephalus due to the partial obstruction of the cerebrospinal fluid outflow tract.

VENTRICULOGRAPHY. This procedure is usually performed by making trephine openings in the posterior parieto-occipital regions. A ventricular needle is inserted into the posterior horn of each lateral ventricle and 10 cc. of gas, usually room air, is injected alternately into each needle, allowing fluid to escape from the opposite needle until no more fluid can be obtained. As is true with the pneumoencephalogram, the resulting contrast study will reveal ventricles in which there is a mixture of gas and cerebrospinal fluid. The gas will rise to the uppermost part of the system, which will in turn be determined by the position of the patient's head. By positioning the patient in brow-up and brow-down positions, right side up and left side up, the major portions of the ventricular system can be visualized. The fourth ventricle and the aqueduct are usually not well seen. The types of abnormalities which intracranial masses may produce are the same as those noted in the section on pneumoencephalography. Most cerebral masses situated outside of the ventricles produce deformities by displacement of the ventricular system to

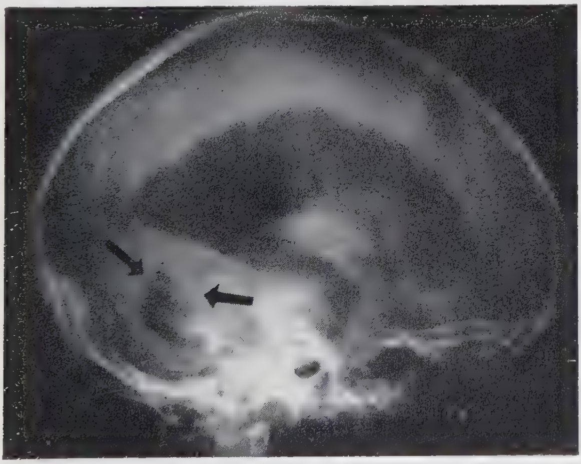


Fig. 2. Lateral projection of pneumogram of same patient cited in Figure 1. More gas has been injected. Widely dilated lateral ventricles, third and fourth ventricles are seen. The arrows indicate the border of the fourth ventricle with tumor mass projecting upward and posteriorly from the floor of the ventricle.

the side opposite the lesion. There may also be some localized deformity of the portion of the ventricle in the neighborhood of the tumor.

Intracranial tumors vary in the degree with which they cause local deformity of the ventricle of displacement of the ventricular system. Displacement of the third ventricle away from the tumor is prominent with tumors of the temporal lobe, but there are less obvious changes in the lateral ventricles. Tumors in the frontal lobe above the lateral ventricle may cause downward displacement of the frontal horns with very little shift of the ventricles to the opposite side. The interpretation of these changes depends on a synthesis of displacement and deformity for proper localization of the mass.

Cerebral Angiography

Since the demonstration by Egas Moniz in 1927 of the technique of cerebral angiography, this procedure has become widely used. The usual cerebral angiogram involves injection of radiopaque material into the internal or the common carotid artery. Angiography may be done by the vertebral artery route, but this is usually not helpful. Displacement of vessels in the posterior fossa is obscure and interpretation of abnormalities is far less accurate than in the supratentorial regions. In some patients with brain tumors both cerebral angiography and pneumograms are necessary for accurate localization and also accurate predictions about the vascularity and cell type of the tumor. The majority of cases may be selected so that either angiography or pneumography will provide adequate information.

The usual cerebral angiogram involves injection of Hypaque into the internal carotid artery. Most examinations require the use of 8 to 10 cc. The injection must be done very rapidly and the first film exposed while the last 1 to 2 cc. are being injected. Films are exposed every 20 to 30 seconds thereafter until 3 or 4 films are taken. Automatic rapid serial filming is desirable in certain cases, particularly when vascular anomalies may be present or when 6 to 10 films may be desired in each plane. Automatic rapid serial filming is useful but requires expensive equipment. It is not essential for the demonstration by angiographic techniques of cerebral tumors.

The roentgen signs of tumors on cerebral angiography are essentially vessel displacement and abnormal circulation. The most important features concerning these two signs are found in the arteriogram as opposed to the venogram phase of the study. Small tumors, of course, may displace the vessels deceptively little. This may present a problem in some instances of frontal lobe tumors. By and large, a mass in the intracranial space will distort vascular structures by the size and location of the mass and by satellite edema. In other instances, abnormal circulation patterns occur within the tumor, as in benign tumors like meningiomas or in highly malignant tumors such as glioblastomas. Figure 3 is a

Fig. 3

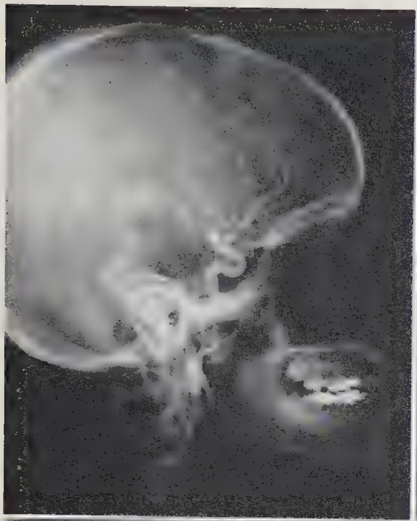
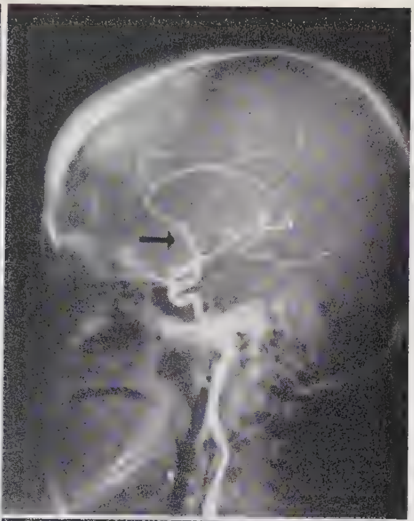


Fig. 4



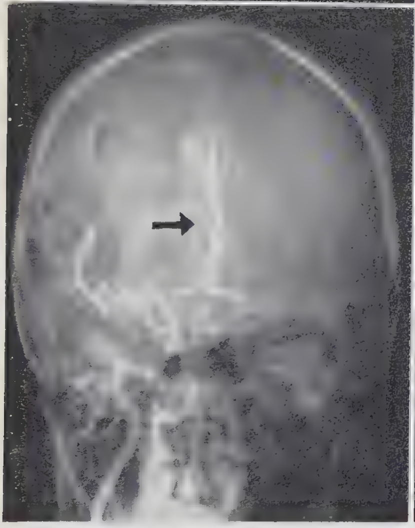


Fig. 5

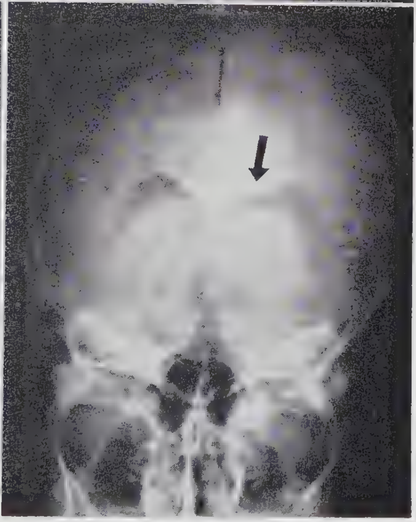


Fig. 6

Fig. 3. Normal right lateral carotid arteriogram for comparison purposes.

Fig. 4. Right lateral carotid arteriogram showing marked posterior displacement of the anterior cerebral artery caused by a right sphenoid ridge meningioma. (Courtesy of Dr. John H. Juhl.)

Fig. 5. Right carotid arteriogram as seen in the anteroposterior projection. The arrow indicates a shift of anterior cerebral arteries (both filling from the right side) across the midline and away from the tumor.

Fig. 6. Pneumoencephalogram in the posteroanterior projection. The arrow indicates depression of the roof of the lateral ventricle caused by a left parietal, convexity meningioma. This is the same patient cited in Figures 7 and 8. (Courtesy of Dr. John H. Juhl.)

normal angiogram in the lateral projection shown for comparison. Figures 4 and 5 are lateral and A-P carotid arteriograms showing obvious displacement of the anterior cerebral artery caused by a sphenoid ridge meningioma. No "tumor stain" or collection of abnormal vessels within the tumor is seen.

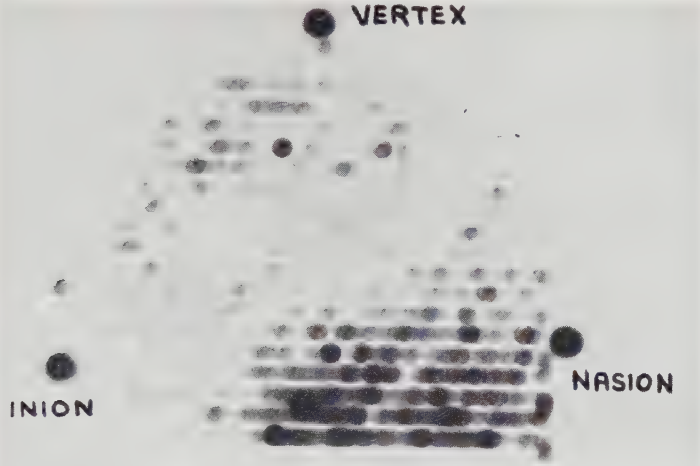
RADIOISOTOPE ENCEPHALOGRAPHY

In the latter part of the 1950's, earlier technical difficulties which had made the use of radioisotopes impractical in localization of brain tumors and other types of intracranial disease were overcome because of rapid advances in technology as well as some important biophysical investigations. At the present time there are two rather different techniques involved in radioisotope brain scanning.

By far the most popular type of brain scanning technique is the use of scintillation scanners. The commercial units which are available at this time are quite satisfactory and make the technique simple. The write-out device which is used most frequently is photographic representation by which means the eye can appreciate differences in count density on the film. The most frequently used isotope is radio-iodinated human serum albumin. This technique using I^{131} involves the intravenous injection of approximately 2.5 microcuries per pound of body weight, or 5.5 microcuries per kilogram of body wieght, 24 to 48 hours before the brain scanning procedure. The maximum dose used is 500 microcuries regardless of the patient's size. Lugol's solution (0.5 cc.) is given orally two hours prior to the injection of the isotope in order to block the uptake of I^{131} by the thyroid gland. Brain scans of the appropriate portion of the head are made at 24 and 48 hours. The most useful projection for the brain scan is the lateral one.

Lesions in the supratentorial area are most likely to be discovered by means of the brain scan. The lower portion of this region, however, may be somewhat obscured because of increased uptake by the temporalis muscle. The posterior fossa structures are also obscured by the uptake of isotope in the long cervical muscles projecting to the occiput of the skull. In diagnosis of tumors of the cerebrum, the accuracy of brain scanning has been impressively high. In one series of 344 patients[18] a total accuracy of 92 per cent was achieved. What is most important, only two false positive results were noted. Other clinics have reported an accuracy of roughly 75 per cent, with a very low incidence of false positives.[10] The value of the test lies not only in its accuracy but also in the low morbidity of the procedure. The test requires comparatively little of the physician's time, although a significant investment of time by the patient and the radioisotope technician and laboratory is involved. The second advantage lies in the fact that brain scans have been found to give more accurate indications of the size of a tumor than either angiograms or air studies. A third advantage is the availability of the procedure for follow-up studies. Since the test is not hazardous, nor is it uncomfortable, it is obviously more practical to repeat the brain scan serially than it is to repeat air studies or angiography. With increasing emphasis on the dangers of radiation exposure, it is obvious that if radioisotope encephalography is going to be used with greater frequency, it will become more and more important that the isotopes used produce

Fig. 7



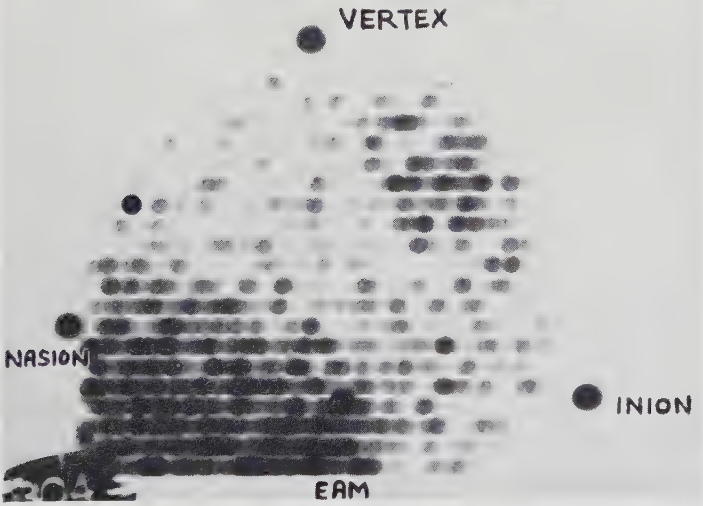


Fig. 8

Fig. 7. Right radioiodinated serum albumin (RISA) brain scan. This is a normal brain scan. (Courtesy of Drs. Joyce C. Kline and John R. Cameron.)

Fig. 8. Left RISA brain scan showing area of increased uptake of the isotope in the left parietal area. This is the same patient shown in Figures 6 and 7. The left carotid arteriogram in this patient was normal. (Courtesy of Drs. Joyce C. Kline and John R. Cameron.)

a low total body exposure and that they not produce any specific damage to organs in which they may be collected. At the present time I^{131} best fulfills these criteria. Radio mercury (Hg^{203}) is an isotope which is used in some laboratories.[2] The technical results from the brain scan using radio mercury are good, but the fact that this isotope is collected in the kidneys and produces a significant radiation exposure to the kidneys is a definite liability in its use. This disadvantage is not completely overcome by the use of blocking substances such as meralluride (Mercuhydrin). Figure 6 is a pneumoencephalogram of a patient with a left parietal meningioma. Figures 7 and 8 are examples of the brain scan in the same patient.

The second type of brain scanning device is the coincidence scanner used with positron-emitting nuclides such as radio arsenic (As^{74})[3] or radio copper (Cu^{64}). This technique is able to detect an area of increased isotopic concentration in the skull at any depth with equal sensitivity. Thus half the time is saved by recording from both sides of the head simultaneously. The objections to the positron scanning type of technique are as follows: (1) The cost is relatively high because of the expense of the isotopes. (2) The technique lacks flexibility in terms of application to other organs of the body, whereas the scintillating scanning devices may be applied for brain scans, liver scans, etc. (3) It is more difficult to interpret the record which the positron scanner produces as compared to the scintillation scanning record. (4) The cost of the basic equipment for the positron scanning is higher than the scintillation scanning equipment. (5) The positron scanning technique produces a relatively high dosage of total radioactivity for the patient. In contrast to the scintillation scanning technique using isotopes such as I^{131} in which the patient receives a total body dose of approximately 0.6 rad, the patient being tested with the usual positron scanning techniques may receive a total body dose of 4.2 rads.

SUMMARY

Tests for brain tumors have been reviewed. The emphasis has been on measures for evaluation of patients which are already widely available or are becoming so. Conventional office and bedside observations are discussed. There is a review of tests which may be conceived as extensions of the neurological examination. These include observations of the visual and auditory systems and the psychological status (neuropsychology). Electroencephalography is emphasized. The final sections deal with neuroradiology and radioisotope encephalography.

Utilization of several or all of the tests or techniques mentioned will produce a high yield of accurate predictions concerning the presence of brain tumors. For those patients whose problem remains obscure after appropriate evaluation, observation of the natural history of the illness

and neurological examinations repeated over several months will provide the most accurate "test" and will indicate the most sensible management.

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Treatment of Brain Tumors

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THE TREATMENT of brain tumors may conveniently be considered under such headings as surgical therapy, radiotherapy and other methods of therapy, such as ultrasonic therapy and chemotherapy. In spite of the many recent advances that have been made in the various forms of treatment mentioned, surgical therapy still remains the primary method of treatment for brain tumors.

Although evidences of trepanation and operations on the head have been found in mummies of ancient Egypt and in the skulls of prehistoric races, such operations have assumed significance only in recent times since it has been possible to diagnose and localize lesions of the brain. The successful development of neurological surgery as a specialty necessarily awaited such primary developments in the field of neurology as neuroanatomy, neurophysiology, neuropathology and clinical neurology. Building on the knowledge provided by the pioneers of early descriptive neurology, Cushing[12] established neurosurgery on a firm basis only following the First World War. The scope and success of neurosurgery were greatly extended by further refinements in such methods of diagnosis and localization as ventriculography,[11] pneumoencephalography,[15] arteriography[17] and electroencephalography.[6] Bailey's[2, 4] basic work on the clinicopathological classification of brain tumors also had important implications with respect to their prognosis and therapy. The debt of neurological surgery to the basic neurological disciplines mentioned cannot be overemphasized and should be clearly stated at the outset.

Of equal importance is the debt of neurological surgery to the basic advances in the field of general surgery asepsis, anesthesia, hemostasis, suction and electrocautery. To this list should be added the Gigli saw and other technical advances in instrumentation, preservation of the blood supply to tissues not excised, the protection of adjacent brain tissues from dehydration, replacement of lost blood by intravenous saline and/or blood, antibiotic therapy, and the use of hypotensive agents and hypothermia. The preoperative care of the patient of poor nutritional status and the temporary shrinkage of the brain by intravenous urea in preparation for emergency surgery may be of great importance in selected patients. Hypertonic solution therapy, however, should be used judiciously, and, aside from the use suggested, ventricular drainage usually is preferred by neurological surgeons. Abnormalities of electrolyte balance must be corrected if found. Postoperative care of the neurosurgical patient, likewise, is of great importance. Keeping the patient quiet, protective bandaging of the head, suction to avoid aspiration of vomitus, bronchoscopy for aspiration of mucous plugs, bowel regulation, catheterization for urinary retention, periodic turning of the patient, and careful nursing care are essential details which the neurosurgeon must be prepared to supervise in the immediate postoperative management of his patients. At a later period, physical therapy is frequently of great help in the rehabilitation of the patient. Its value in improving strength, re-education of function, reducing spasticity and contractures, stimulation of the circulation, and improving the psychologic outlook often make the difference between successful rehabilitation and a vegetative existence.

RADIOTHERAPY

The radiotherapy of brain tumors should never be undertaken without prior histologic diagnosis, except in those cases in which the diagnostic studies have convincingly confirmed the presence of a tumor and then only when the tumor is in an inaccessible region which precludes successful exploration and biopsy. Since tumors such as the cystic astrocytoma of the cerebellum in childhood, which can be cured by surgical excision, may be mimicked by tumors such as the medulloblastoma, which cannot be cured either by surgery or radiotherapy, radiotherapy alone in such cases may result in tragic errors.

Radiotherapeutic success depends upon the differential between the radiosensitivity of the particular tumor and the radiation tolerance of the brain in the treated volume. Here again, determination of the histologic type is of great importance.

Unfortunately, radiotherapy is rarely curative, and successive doses of radiation, even in those patients in whom excellent results have been obtained initially, are rewarded by progressively poorer results. For this reason, the current practice of most therapeutic radiologists involves one thorough course of irradiation, not to be repeated.[8] The trend is toward larger radiation fields, since there is evidence to suggest that some of the past failures may be due to inadequacy in this respect. However, the limitation of all radiation therapy lies in the inability of a directed beam of energy to destroy the invasive extensions of the more infiltrative types of brain tumors without destroying excessive amounts of neighboring normal brain tissue. Thus, therapy short of the point of incapacitating the patient is rarely curative.

Radiation Methods

Because many tumors diffusely infiltrate the brain or are in locations which render them inoperable, x-ray therapy is frequently used either alone or as an adjunct to surgery. Pinealomas, for example, in which the surgical mortality is very high and in which surgery is followed by seeding of the tumor cells throughout the ventricular and subarachnoid spaces, and medulloblastomas, which are radiosensitive and in which seeding also occurs, are commonly treated by radiotherapy alone. Glioblastomas, craniopharyngiomas and some meningiomas, on the other hand, are relatively irresponsive to standard radiotherapy. Nevertheless, because of the poor results of surgery in glioblastomas, x-ray therapy is used by some, either alone or following surgery, in an effort to retard progression. In some craniopharyngiomas postoperative radiation therapy has accomplished prolonged arrest. Other tumor types, such as the cellular forms of meningiomas, some astrocytomas, spongioblastomas, oligodendrogliomas and hemangioblastomas, are moderately responsive to radiotherapy and may significantly be retarded by its use. In the responsive pituitary adenomas, radiation therapy affords consistently effective results and constitutes the definitive method of treatment. Neuroblastomas are very responsive and judiciously used radiation therapy may be curative.

The x-ray therapy of brain tumors is subject to the same technical problems as x-ray therapy elsewhere. To overcome the usually small difference in radiosensitivity between tumor tissue and neighboring normal tissue, multiple portals or rotational therapy is used to disperse the dose to normal structures while concentrating the dose on the tumor.

Tumor dosage of approximately 5000 rads administered in 25 to 30 treatments over a period of not less than 5 to 6 weeks and through multiple portals is generally accepted as adequate treatment for most types of brain tumors. Doses beyond this may be complicated by cerebral atrophy,[7] whereas smaller doses may fail to afford the patient the maximal benefits of such therapy. The details of therapy must be decided by the roentgen therapist in collaboration with the neurosurgeon and will vary depending upon the location and size of the tumor, the type of x-ray equipment available, and the tolerance of the patient to radiation.

Investigative Methods of Radiation Therapy

Supervoltage and Megavoltage Therapy. The value of very high voltage therapy of brain tumors is at present being investigated. Various techniques, including the cobalt bomb (gamma ray equivalent to x-rays from a 3000 KV apparatus), betatrons, linear accelerators, synchrotrons and cyclotrons (up to 70,000 KV and much higher in the case of the cyclotron), are being used. The effects of radiation therapy on the skin are less and the patient's general reaction is usually less from megavoltage therapy than from 250 KV therapy. Although high voltage radiation has the advantage of greater penetrability (radiations of 1000 KV and over readily penetrate bone) and of delivering the desired dose to deep targets with minimal doses to overlying tissues, the total tumor dose cannot be increased beyond that already mentioned, because of the effect of such therapy on the tissues more deeply situated or beyond the tumor.

Electron Beam Therapy. Better therapeutic results per unit of energy in the dose delivered have been claimed for the beta ray, or electron beam therapy, as compared with the usual gamma radiation. Although advantageous for superficial tumors, the technique is limited with respect to deep therapy. 20,000 KV electrons are effective up to a depth of 5 cm., but the advantage of this method falls off with higher voltages and greater depths.

Radioisotopes. The biological ionizing effects of radioisotopes are similar to those of x-radiation, and their effectiveness depends, in large measure, upon the differential concentration of the isotope in the tumor, as opposed to other surrounding tissues.[18] Although the tumor may initially attain high concentration of radioactivity with parenterally administered isotopes, a specific and lasting localized effect cannot be maintained, since the isotopes are eventually distributed to the other tissues of the body. This limitation may be obviated by the direct injection or implantation of radioactive compounds, or of radon seeds, into the tumor. In this case an insoluble form of the isotope, such as colloidal chromic phosphate (P^{32}), is used, since it is not available for vascular absorption and distribution to other parts of the body. However, this method presents problems similar to those encountered in the treatment of carcinoma with radium and, like this older technique, will probably have similar limitations.

ULTRASONIC THERAPY

In this method a high-frequency vibration of high energy is produced electronically and transmitted through a liquid junction, making direct contact with the brain. Since it is feasible within certain limits to "focus" the energy of such ultrasonic beams, the possibility of utilizing this technique for the destruction of tumor tissue is being investigated. The limitations of this technique, however, are considerable, since it requires the removal of the overlying skull and effective doses may be destructive to overlying normal brain tissue. Such limitations make the use of ultrasonic techniques impractical, at least in their present form.

CHEMOTHERAPY

The literature on chemotherapy for brain tumors is very limited and largely devoted to experimental work on animals and tissue cultures. Studies on patients with essentially hopeless brain tumors, chiefly glioblastoma multiforme and metastatic tumors, have been initiated in several centers, but in general the results have been discouraging. It has been shown that normal cerebral tissues, and in particular the cerebrovascular system, are sensitive to nitrogen mustard and similar antimitotic chemical agents. Their toxic effects have made their use by perfusion impractical. However, occasional patients have shown a good response to nitrogen mustard administered systemically (0.4 mg. per kilogram of body weight, intravenously).

Several other agents, such as Methotrexate (4-amino-N^{10}-methylpteroylglutamic acid) and Vincristine ($C_{46}H_{54}N_4O_{10}\cdot H_2SO_4$) and the related agent Vinblastine are at present being tested and have the advantage of being less toxic to the brain than nitrogen mustard. Regional perfusion and intracarotid infusion on the side of the tumor have been used with the hope of concentrating the dose of the chemotherapeutic agent in the region of the tumor. Added advantage has been gained in the use of Methotrexate by the intravenous injection of citrovorum factor, a nontoxic antagonist, which when given at the same time as the arterial injection of Methotrexate, serves to further reduce systemic toxicity.[25] Although the effects of some of the newer chemotherapeutic agents have not yet been adequately evaluated, the results with those which have been tried over the past few years have been rather unpredictable and palliative at best. Unfortunately, the therapeutic index of chemotherapeutic agents for brain tumors would appear to be low, so that even effective palliative doses are close to their toxic dose levels. Because of this, it would appear that the problem in chemotherapy, as in isotope therapy, is concerned with obtaining an effective concentration of chemotherapeutic agents in tumors. If the differential concentration of such agents in the tumor, as compared with the concentration in other portions of the brain, is not sufficiently great, either an effective therapeutic dose for the tumor is not achieved or a dose which is too toxic to the other tissues is delivered. Unfortunately, differential concentrations of the degree required cannot be maintained with the present agents. The problem would appear to require a high initial concentration of an antimitotic agent in the tumor which would be transformed as a result of its reaction with the tumor or by other means into an insoluble compound which would resist reabsorption and transport away from the tumor. This basic problem in both isotope therapy and chemotherapy has not been solved.

In summary, present evidence indicates that chemotherapy can in no sense be considered curative. However, because sporadic palliative results have been achieved, investigative chemotherapy is justified in those patients with brain tumors which have failed to respond to all standard modes of treatment.

THERAPY OF SPECIFIC ENTITIES

The success of therapy of brain tumors varies widely depending upon their type, size and location. Accordingly, the plan of therapy must be adjusted to each patient only after a complete study which takes into consideration the differences indicated as well as the availability of special professional personnel and technical modes of therapy.

Although 85 per cent of all brain tumors occur in adult life, certain types are peculiar to childhood, so that other considerations are introduced that must be taken into account. The incidence data used in the following sections are based upon eleven large series of brain tumors in adults and six large series of brain tumors in childhood reported in the literature.[1]

Gliomas

Astrocytomas

Astrocytomas of the Cerebrum. These tumors, which constitute nearly 17 per cent of all adult brain tumors, are of widespread distribution and may involve deep cerebral structures as well as the cortex. The majority, however, are situated in part or *in toto* in the frontal lobes.[19] Astrocytomas tend to be avascular and infiltrate adjacent cerebral tissue.

The resectability of astrocytomas is limited by their infiltrative character and location. If situated in one frontal lobe or in the nondominant temporal or occipital lobe, effective resection is usually possible. Because they rarely can be resected *in toto* and commonly extend across the midline, recurrence is the rule. This is particularly true of the noncystic and more infiltrative astrocytomas located subcortically in the dominant hemisphere. The rare cystic astrocytoma, if located in the nondominant hemisphere, on the other hand, has the most favorable prognosis, and a cure may be achieved if the mural nodule is resected.

Although astrocytomas are relatively irresponsive to x-ray therapy, it is commonly used postsurgically in the hope of retarding recurrent growth. Radical surgery, repeated if necessary and when possible, plus x-ray therapy may extend the patient's life for several years. The average survival period for all astrocytomas approximates three years. Survivals well beyond this period, however, are common in more favorable cases that are well handled.

Astrocytomas which cannot be treated effectively by the usual surgical and x-ray techniques have been the subject of such investigative therapies as megavoltage x-rays, radioisotope therapy and chemotherapy.

ASTROCYTOMAS OF THE CEREBELLUM. Astrocytomas of the cerebellum are usually cystic and have their highest incidence in childhood between the ages of 7 and 12. They constitute more than one fourth of the brain tumors of children. Complete removal of the mural nodules or plaques of tumor tissue results in a cure and this group constitutes one of the brightest chapters in the neurosurgical treatment of brain tumors. With incomplete removal of the mural nodule or with the noncystic type, the tumors almost invariably recur Because these tumors are not responsive to roentgen therapy, their course largely depends upon their pathologic type and how effectively they can be handled surgically.

Glioblastoma Multiforme (Spongioblastoma Multiforme)

Glioblastomas have essentially the same incidence as the astrocytomas of adult life and in adults constitute nearly one sixth of all brain tumors and more than one third of all gliomas. About two out of three glioblastomas occur in men. Their incidence in children is considerably less (5.8 per cent). They are found very largely in the cortex and have a particular tendency to occur in the frontal, parietal and temporal lobes.[20] Glioblastomas are associated with a rapid clinical course, are usually large tumors by the time they come to surgery and grossly infiltrate the adjacent gray and white matter. They have been found to infiltrate across the midline via the corpus callosum in about one half of all patients.

Glioblastomas are usually fatal within 12 to 16 months regardless of the type of therapy used. Removal of as much of the tumor as possible and x-ray treatment are generally practiced for glioblastomas in the nondominant hemisphere. Many surgeons now merely take a biopsy specimen of the tumor through a trephine opening when a glioblastoma in the dominant hemisphere is suspected and go no further if the biopsy confirms the diagnosis. X-ray therapy is of doubtful worth, but some workers feel that it has palliative value when given in large doses –over 4000 rads. Since rare survivals for five and even ten years have been reported, some neurosurgeons deplore the usual defeatist attitude which has developed toward glioblastomas. They advocate resection, as drastically as can be performed with adequate retention of function, to be followed by x-ray therapy.[24] Because of the poor results usually achieved by the standard methods of treatment, megavoltage x-ray therapy, radioisotope therapy and chemotherapy for glioblastomas are being investigated actively.

Medulloblastoma

This very malignant tumor, which arises from the posterior lip of the posterior medullary vellum of the fourth ventricle, occurs almost invariably in children.[2] It constitutes 18 per cent of the tumors of childhood and involves boys in some 70 per cent of cases. The rare medulloblastoma of adulthood runs a much more benign and chronic course.

Surgical exploration is required to confirm the diagnosis and to rule out such other tumors as cystic astrocytoma of the cerebellum, found in approximately one fourth of all children with brain tumors. Needle biopsy has been advocated as a substitute for surgical exploration. If the diagnosis of medulloblastoma is confirmed, x-ray therapy should be given. Since x-ray therapy produces an initial dramatic improvement in nearly all cases, the need for suboccipital decompression prior to x-ray therapy has been debated. Because early recurrence and progressive irresponsiveness to radiation therapy end fatally within one to two years in the great majority of cases, more recent practice has involved an initial delivery of maximal x-ray doses to medulloblastomas and no further radiation therapy with recurrence of the tumors. As with glioblastomas, various forms of investigative therapy are being tried.

Ependymomas

These tumors constitute only some 2 per cent of all adult tumors but nearly 10 per cent of the tumors of childhood. They usually arise in the ependyma of the third and fourth ventricles. Those which occur in the cerebral tissue (presumed to have a relation to the lateral ventricles) are more common in childhood, grow more slowly and are apt to calcify.

The deep location and vascularity of these tumors greatly increase their surgical risk. Except for those limited to the choroid plexus, they cannot be removed completely. Since they are also relatively irresponsive to radiation therapy, the usual survival period of patients with these tumors is from two to four years. Although the newer investigative modes of therapy are being tried in selected patients with ependymomas, the low incidence of these and the other gliomas discussed in subsequent paragraphs tends to preclude the collection of sufficiently large groups of cases necessary for scientific evaluation.

Spongioblastoma Polare

Polar spongioblastomas are slow-growing tumors found mainly in the region of the third ventricle, optic chiasma and brain stem. They occur in 1.8 per cent of adults and in nearly 5 per cent of children with brain tumors. Their surgical removal is usually impossible. It is important to distinguish the brain stem variety from extramedullary tumors of the posterior fossa, such as meningiomas and cysts, since the latter can be dealt with more effectively surgically.

The usual treatment of polar spongioblastomas following their surgical confirmation is x-radiation. This frequently is effective in prolonging life and in improving the patient's clinical condition.

Oligodendrogliomas

These tumors occur in 1.4 per cent of adults and in nearly 2 per cent of children with brain tumors. Some 14 per cent of these tumors arise infratentorially and 10 per cent in the basal ganglia or region of the third ventricle. The remainder are largely frontal or extend posteriorly to involve the adjacent parietal and temporal lobes. They tend to spread bilaterally via the corpus callosum and at least 50 per cent occur in deep structures. The oligodendrogliomas grow slowly and in this respect are similar to the astrocytomas.

The treatment of these tumors is similar to that described for the noncystic astrocytomas. The rare oligodendrogliomas which involve the vital structures of the brain stem, however, have a very poor prognosis.

Astroblastomas

Astroblastomas occur in about 1.6 per cent of adults with brain tumors and are rare in children. Because these tumors are more malignant than astrocytomas, their treatment by means of surgery and x-ray is similar to that for glioblastoma multiforme.[16] Their prognosis, however, of three or more years is distinctly better than that of glioblastomas.

MENINGIOMAS

The incidence of tumors of the meninges is 17.4 per cent in adults and 3.8 per cent in children. Approximately 60 per cent occur in women. Although they vary widely in their rate of growth, the usual clinical course is of considerable duration. Correspondingly, the underlying brain adjusts to their presence and cortical dysfunction develops relatively late when they have grown to large size. Convulsions, which are commonly focal, frequently are the first manifestation of meningiomas and may develop years before increased intracranial pressure or other neurologic signs and symptoms.

Approximately 30 per cent of meningiomas occur in the *parasagittal* area and about 20 per cent in *other areas over the convexities*. The remainder are found chiefly at the base of the brain, along the sphenoid ridges, in the olfactory grooves, or near the midline in the suprasellar region and the anterior face (clivus) of the posterior fossa.

Surgical treatment of the parasagittal and convexity meningiomas in the adult yields results which are among the most satisfactory obtained by the neurological surgeon.[13, 22] However, the usual marked vascularity of these tumors, their great size which often precludes removal of the tumor and its capsule *in toto*, and their not infrequent involvement and infiltration of the cavernous sinuses and skull, present the surgeon with great difficulties in a high percentage of cases.

Preoperative angiograms to define the vascular supply and drainage of these tumors, preliminary ligation of their vascular supply or even ligation of the external carotid artery in selected cases, and the modern use of hypotensive agents and hypothermia have greatly extended the surgeon's ability to deal effectively with these tumors. Preoperative x-ray therapy also has proved effective in reducing the vascularity of meningiomas.

When these tumors are malignant, invasive and inaccessible, as they are likely to be in children, surgical results are far more disappointing and x-ray therapy becomes the treatment of choice. However, except in the more uncommon cellular types of meningiomas, which grow more rapidly and which are more invasive, these tumors usually do not respond well to x-radiation. Repeated operations are required for the usual recurrent types and may afford patients many years of useful life.

EXTRINSIC TUMORS

In one sense all intracranial tumors, other than the gliomas, might be defined as extrinsic tumors. This term, however, ordinarily is confined to such tumors as metastatic tumors, eosinophilic granulomas, osteomas, chondromas, and other extrinsic invasive tumors. Eight per cent of all adult tumors and 1.3 per cent of the tumors of childhood fall into this category.

Metastatic Tumors

Metastatic tumors constitute approximately one half of the entire group of extrinsic tumors of the brain. The most common sources of these tumors are lung (26 per cent), breast (20 per cent), genitourinary system (11 per cent), and gastrointestinal system (7 per cent). They often appear before the primary tumor is recognized.

The treatment of metastatic tumors of the brain must obviously be considered in conjunction with the treatment of the primary lesion. If a single lesion is demonstrated by the clinical study, exploration is often indicated, depending upon the general condition of the patient. Palliative measures (surgery and x-ray) may extend the useful life of the patient.

Eosinophilic Granulomas

Eosinophilic granulomas usually appear as punched-out skull lesions. They are thought to be local manifestations of, or closely related to, such generalized metabolic disturbances as xanthomatosis (Hand-Schüller-Christian syndrome or Letterer-Siwe's disease). Therapy consists of surgical excision, clean curettement and follow-up x-ray therapy.

Invasive Tumors of the Base of the Skull

The invasion of nasopharyngeal carcinomas and of sarcomas from the paranasal sinuses and middle ear cavities to inaccessible regions at the base of the brain presents a serious and essentially hopeless problem. These constitute 1 per cent of adult tumors. Ventriculocisternostomy and palliative radiotherapy constitute the only available therapies for these tumors. Because of their malignant nature and inaccessibility, a trial of the various investigative therapies would appear to be well justified.

ACOUSTIC NEURINOMAS (PERINEURIAL FIBROBLASTOMAS)

Acoustic nerve sheath tumors are the most common tumors of the cerebellopontine angle and constitute 7 per cent of all adult brain tumors.[9] They are rare in childhood.

Cerebellopontine angle tumors usually start with tinnitus and progressive deafness on one side, followed by facial hypesthesia, other neighboring cranial nerve signs, and cerebellar involvement on the same side. Increased intracranial pressure and long tract signs develop later. Erosion of the internal auditory meatus, a cerebrospinal fluid protein over 100 mg. per 100 ml. and a failure of filling of the basal cisterns on the suspected side by pneumoencephalography are the most useful laboratory diagnostic aids. Acoustic neurinomas are occasionally bilateral and may be associated with von Recklinghausen's neurofibromatosis. Meningiomas, gliomas, aneurysms and, more rarely, other tumors in or near the cerebellopontine angle can mimic the acoustic neurinomas.

Surgical extirpation is the treatment of choice for acoustic neurinomas, since they are not responsive to radiotherapy. Although intracapsular removal of as much of the tumor as possible is less hazardous and produces fewer residual cranial nerve deficits and vascular complications of the pons, some neurological surgeons favor complete removal of the tumor whenever possible on the grounds that recurrences usually follow incomplete removal and that second operations for acoustic neurinomas carry a high mortality rate. Since these tumors may be removed completely, if recognized early, it is doubly important that physicians be alert to their development, which in the early stages may involve a slow progression in the loss of cranial nerve VIII function alone.

PITUITARY ADENOMAS AND CRANIOPHARYNGIOMAS

Although their clinical manifestations are different, these tumors, because of their location, may justifiably be considered together from the standpoint of their treatment. Pituitary adenomas constitute about 10 per cent of adult and 2 per cent of childhood tumors. The incidence of craniopharyngiomas is almost exactly the reverse: over 10 per cent in children and over 2 per cent in adults.

Pituitary Adenoma

Three types of tumor may arise from the pituitary gland and each differs in its clinical picture:

Chromophobe adenomas, which constitute 80 per cent of adult pituitary tumors (but are rare in childhood), produce anterior pituitary deficiency (eunuchoid picture in the male, amenorrhea in the female, loss of energy, etc.) because of their destruction of acidophil cells. Visual field defects, most commonly of the bitemporal type, are usually associated with this tumor.

Chromophil (acidophilic) adenomas cause disturbances of anterior pituitary hyperfunction, gigantism in children, and acromegaly after normal growth has been attained. Visual field defects are less severe.

Basophil adenomas, which are exceedingly rare, cause the endocrine changes of Cushing's syndrome, but no neighborhood pressure effects.

Craniopharyngiomas

Craniopharyngiomas are congenital tumors and arise from the embryonic Rathke's pouch region in either the intrasellar or suprasellar position. Twenty per cent are cystic and most contain adamantinomatous or tooth-forming tissue. Endocrine deficiency states are produced, depending upon which pituitary or neighboring hypothalamic structures are encroached upon. Diabetes insipidus develops in about one fourth of all patients. Visual field defects are common and occur early. Whereas pituitary adenomas are calcified in only some 10 per cent of cases, craniopharyngiomas show calcification in 70 per cent.

Treatment

Surgical removal is the preferred treatment for these tumors when sight is threatened. A transfrontal craniotomy on the side of the nondominant hemisphere is the usual approach, but it may be complicated if the chiasm is prefixed. Preoperative evaluation of endocrine function is requisite and hormonal replacement therapy should be instituted for any deficiency that has been demonstrated.[11] ACTH or cortisone is commonly given before and during surgery and is continued in maintenance doses if the pituitary-adrenal system is permanently damaged. Abnormalities of electrolyte metabolism are particularly prone to occur in patients with tumors involving the hypophysis and hypothalamus and should be corrected preoperatively, if present.[5] It is also essential that a proper electrolyte balance be maintained postoperatively to ensure satisfactory recovery. Because surgical excision of these tumors in their entirety is but rarely possible, recurrence is common; the principal achievement of surgery is the decompression of the optic pathways and neighboring hypothalamus.

Surgery, combined with x-ray treatment and hormone substitution when necessary, has afforded the best results in chromophobe adenomas and craniopharyngiomas. The acidophilic and basophilic tumors of the pituitary less frequently require surgery.

Radiotherapy is the treatment of choice for all pituitary tumors if endocrine disturbances are their only manifestation and if the diagnosis can be clinically substantiated.

BLOOD VESSEL TUMORS

Angiomas

These arteriovenous anomalies of cerebral circulation occur in over 2 per cent of both adult and childhood cases of brain tumors, although this incidence may be low since it was based on large series prior to angiography.

Treatment depends upon the occlusion of their arterial blood supply or, when possible, their excision. The anastomotic collateral circulation of angiomas usually renders ligation of their carotid supply of little or no value. Preoperative arteriographic study is mandatory, as is an adequate supply of whole blood for administration at the time of surgery. Hypothermia and/or hypotensive agents, when indicated, have greatly lessened the hazards and extended the scope of neurosurgical treatment of these lesions.[21]

Hemangioblastomas

Tumors of the blood vessels are largely confined to the posterior fossal and are frequently associated with congenital abnormalities. Von Hippel-Lindau's disease consists of retinal hemangiomas associated with cerebellar hemangioblastomas. Lindau's disease may include cysts of the pancreas and kidneys. These tumors constitute less than 1 per cent of adult brain tumors and are rare in childhood.

Hemangioblastomas of the cerebellum are usually cystic and, as with cystic astrocytomas, surgery is curative in the sense of preventing recurrence, provided that the mural nodule can be removed. Some 40 per cent of patients with cerebellar hemangioblastomas have been found to have an associated polycythemia, which clears with their surgical removal.[10] The solid *hemangioblastomas of the medulla,* on the other hand, are essentially inoperable because of their vascularity and location. Unfortunately, hemangioblastomas usually are not responsive to roentgen therapy. Investigative forms of therapy are presently being tried on the tumors.

MISCELLANEOUS TUMORS

Infectious granulomas (syphilitic, tuberculous, torulosis, schistosomiasis, mycoses, etc.), pinealomas, papillomas of the choroid plexus, etc., constitute a residual 5 per cent of adult tumors but some 18 per cent of the tumors of childhood.

Specific drug therapy for *granulomas* is indicated when available, along with their surgical extirpation when this is possible.

Pinealomas (4 per cent of childhood tumors and rare in adult life) are best treated by ventriculocisternostomy and x-ray therapy, since the great majority of these tumors are inoperable.[23]

Papillomas of the choroid plexus should be surgically removed as completely as possible and subjected to follow-up x-ray therapy.

CONCLUSION

Although rarely malignant in the sense of their metastatic potentialities, brain tumors carry a serious prognosis because of their location and involvement of vital functions. Their prognoses vary widely depending upon their type and location. Even though the ultimate solution of the brain tumor problem must await an understanding of tumor growth in general, modern means of therapy achieve brilliant results in many cases. Each tumor-suspect patient must be studied with care, if early diagnosis is to be achieved, if the patients with good prognoses are to be sifted out, and if the best therapeutic results are to be attained in each case. This may be accomplished, however, only if the physicians who originally see these patients are alert to the potentialities of modern methods of diagnosis and therapy.

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Behavioral Disorders and Brain Dysfunction

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"THE PRE-EMINENCE of the human race in the control of the forces both of inorganic nature and of plant and animal life is undoubtedly directly correlated with the presence and psychological dominance of these higher cerebral centers. Of this there can be no question." Herrick[14] writing in 1924, was referring to those parts of the cerebral cortex that are specifically human.

Other investigators before and since Herrick have established that the nervous system is the phylo-ontogenetically-evolving, ever-more-complex organ of animal behavior.[1, 2, 7, 8, 11, 36] Conel[7] defined behavior as the use of muscle, and muscle use is regulated by the nervous system. In Conel's words, "All behavior, including morals, is on last analysis, the use of muscle. Behavior undergoes development with advancing age and training in the use of the muscles, and the quality of morals in behavior enters when the individual voluntarily directs the use of his muscles for benefit or harm to himself or other humans."

Neurology, the specialty within medicine specifically concerned with disorders of the nervous system, long ago established its interest in and responsibility for the diagnosis, treatment and prevention of disorders of human behavior. This concern of neurology for the understanding of human behavior has been supported by the studies of Bailey,[3] Charcot,[4] Cobb,[5, 6] Flechsig,[9] Foerster,[10] Head,[13] Jackson,[15] Mackay,[20] Magoun,[21] Penfield,[23] Wolff,[27] Yakovlev[36] and many others.

A physician would not undertake to diagnose, prevent or treat a cardiac disorder without a knowledge of the structure and function of the heart; neither could he intelligently and scientifically diagnose, prevent or treat behavioral disorders *as a physician* without a knowledge of the structure and function of the organ of human behavior, the human brain.

The following concepts may seem academic, but they are basic in correlating structure and function of the nervous system with behavior.

First, compared to all other organs (gonads excepted), the human

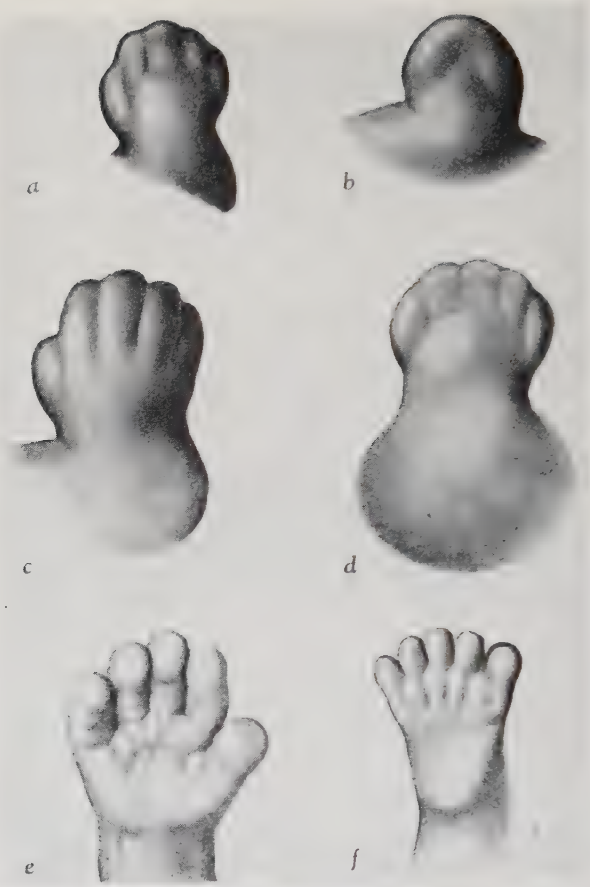

Fig. 1. Ontogenetic development of the human hand (left) and foot (right) at 6 weeks (*a* and *b*), 7 weeks (*c* and *d*) and 8 weeks (*e* and *f*) of intrauterine life. Note that hand development is more advanced than foot development at each chronologic stage. (From Gesell, A.: The Embryology of Behavior. New York, Harper and Bros., 1945, by permission.)

brain at birth is a relatively embryonic structure. Understanding the anatomic and physiologic growth of the nervous system according to its phylo-ontogenetic pattern makes possible the understanding of behavior from birth throughout life.

The nervous system differs from other organs of the body in a second and unique manner. Other organs of the body are functionally concerned with the internal environment of the body. The brain is not only the integrator of the internal body structures but is also equally concerned with adaptation to the external environment. The nervous system accomplishes, by correlation of input from exteroceptive receptors and coordination of output through the efferent nerve systems in the regulation of the musculoskeletal riggings, the adjustment of the body to the external world (i.e., behavior). To quote Conel:[7] "The cerebral cortex is the

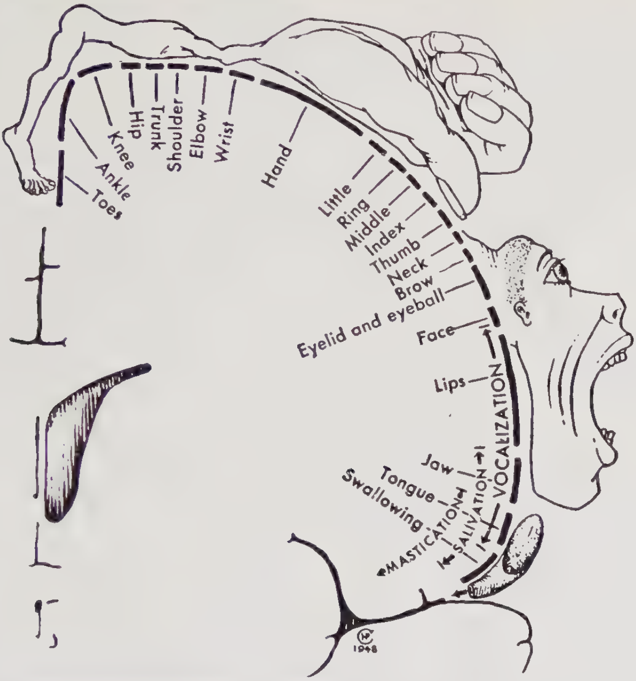
Toes
Ankle
Knee
Hip
Trunk
Shoulder
Elbow
Wrist
Hand
Little
Ring
Middle
Index
Thumb
Neck
Brow
Eyelid and eyeball
Face
Lips
Jaw
Tongue
Swallowing
MASTICATION
SALIVATION
VOCALIZATION
1948

Fig. 2. A cartoon representation of the more complex sensory and motor correlation and coordination supralimbic neural patterns of the human hand and fingers, oral and facial muscles, as compared with the neural patterns of the more proximal parts of the upper extremities, the trunk and the lower extremities. (From Penfield, W. and Rasmussen, T.: The Cerebral Cortex of Man, New York, The Macmillan Co., 1950, by permission.)

highest center in the brain and it is especially concerned with adjustment of the body to the external environment by controlling the striated muscles. Man has risen above all other animals in the phylogenetic series by increasing control of the striated muscles, particularly those involved in speech and the use of the hand."

These two concepts are dramatically demonstrated by combining an illustration from Gesell[11] (Fig. 1) of the ontogenetic unfolding of the hand and foot of the human embryo with an illustration by Penfield and Rasmussen[23] (Fig. 2) of an homunculus placed over the motor and sensory central gyri of the human brain. The increasing complexity of the embryonic unfolding of the terminal portions of the human extremities, particularly the hands and fingers (Fig. 1), is not unlike the musculoskeletal complexity of the hand and fingers of the lower primates The efficient, more complex and intricate use of the striate muscles of the hands and fingers in man is not because the extremities are structurally more complex but primarily because of the unfolding complexity of the supralimbic system of the human brain.

As a further elaboration of the foregoing, the most important function of the human nervous system in relation to the external world is the reactive behavior of one individual to another. This has been simply and objectively illustrated by Cobb[5] (Fig. 3).

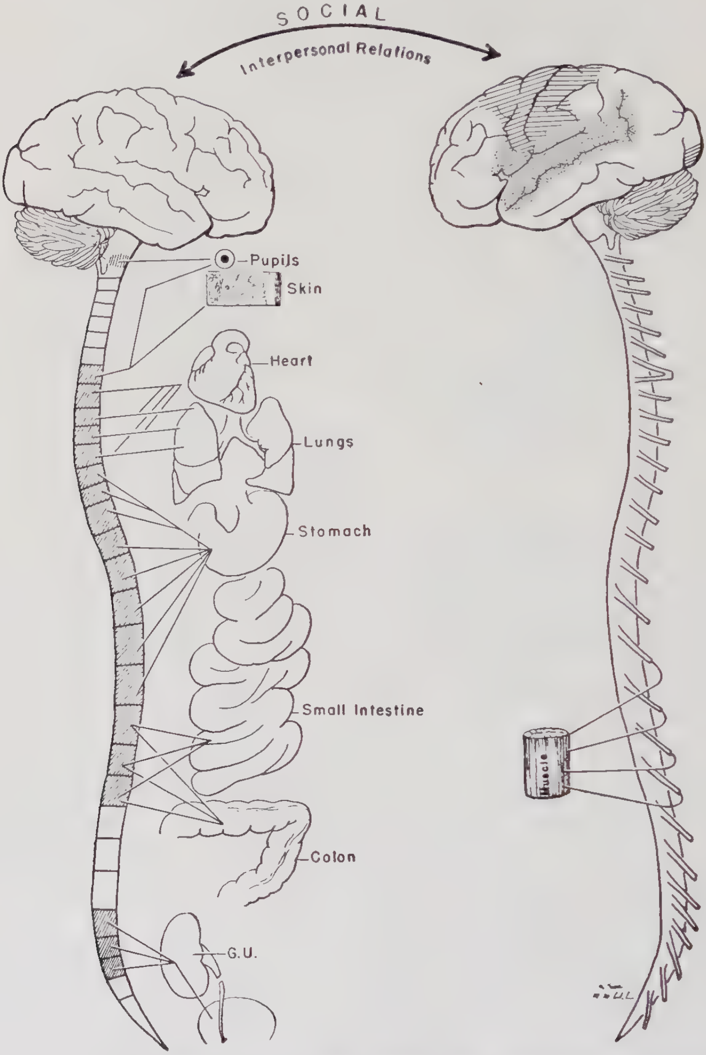

Fig. 3. Social awareness and behavior neurologically and diagrammatically simplified. One CNS reacts upon another, resulting in the development of enormous new possibilities through *interpersonal relations*. The CNS on the left represents the inner (private) smooth muscle visceral behavior. The CNS on the right represents the relationship of the cortical symbolic (stippled), cortical association (white) and cortical projection zones (parallel lines) of the supralimbic system to the final common path in the regulation of the striate muscles resulting in behavior of manufacture and language. (From Cobb, S.: Borderlands of Psychiatry, Cambridge, Mass., Harvard University Press, 1943, by permission.)

A FRAME OF REFERENCE FOR UNDERSTANDING HUMAN BEHAVIOR

During many years of unique clinical experience in following patients with behavior disorders to the postmortem table, and by gross and serial section histologic analysis of the central nervous system (CNS), Yakovlev[28–38] has formulated a useful frame of reference for the correlation of human behavior with the phylo-ontogenetic structural unfolding of the human brain (Table 1).

According to this concept, the continual evolvement of the relatively simple human behavior from birth to the progressively more complex behavior in reaction to the external environment is paralleled by the continuing postnatal ontogenetic evolvement of the human brain in time and space.

Yakovlev describes three human ontogenetic CNS systems in relation to their effector control of the behavior-creating body structure; i.e., muscle. Structurally, these three systems (summarized in Table 1 and illustrated in Figures 4 and 5) are:

1. The rhinic system, which contains the olfactory bulb and tract, anterior perforated substance, pre-optic area, mammilary body, fornix, and the Ammons horn with the hypocampus and amygdala.
2. The limbic system, containing the cingulate gyrus, hypocampal gyrus, uncus, island of Reil, striate-pallidum complex, and the primary motor and sensory projection zones. These projection zones are actually the transitions or extensions of the limbic system into the supralimbic system.
3. The supralimbic system, which includes the association areas of the cerebral cortex (Figure 4—Brodman's postcentral zones 5, 7, 18, 19, 20, 37, 39 and 41) and the precentral association cortex (Figure 4—Brodman's zones 8, 9, 10, 11, 39, 41, 44, 45 and 46).

The rhinic system, being the oldest and adjacent to the neural tube, is the first to evolve. It consists of midline placed, random and intersegmentally arranged neurons, whose functions are confined to the regulation of the midline organs; i.e., the oral, chest and abdominal viscera. The rhinic system responds to visceral sensations and regulates the smooth muscle effectors of the internal environment. Its affector (input) system receives no direct stimuli from the external environment. The function of the rhinic system is strictly private; there is no public behavior, including communication. This is the approximate stage of behavior of the human fetus during the first trimester of intrauterine life and of the idiot (IQ 25 or less), who is unresponsive to objects or persons about him. A fetus or an idiot reacts only to the stimuli of his internal environment.

The limbic system evolves from the rhinic system when the animal begins to express its private internal needs to the external environment.

Table 1

SYSTEMS	RHINIC	LIMBIC	TRANSITIONAL	SUPRALIMBIC
	Random and later evolved nucleate neuronal division	Nucleated and later evolved striate laminated divisions	Limbic to supralimbic	Striate-laminate
1. Neuroanatomic orientation (Fig. 4)	Olfactory tubercle Anterior perforate substance Preoptic area Mammilary body Hippocampus Amygdala	Cingulate gyrus Hippocampal gyrus Uncus Island of Reil Striate-pallidum	Primary motor and primary sensory projection zones (Brodman's areas 4, 6, 8, 43 [motor]; 41 [island of Reil]; 1, 2, 17, 22 [sensory]); striatum (Fig. 4).	Postcentral association cortex (Brodman's zones 5, 7, 18, 19, 20, 37, 39 and 40); Precentral association cortex (Brodman's zones 8, 9, 10, 11, 39, 44, 45, 46 and 47) (Fig. 4).
2. Nerve fiber pattern (Fig. 5)	*Random* arrangement. Crossed and uncrossed fibers not definable—relatively unsystematized.	Fibers in *series*, longitudinally oriented, between nuclear masses of neuraxis.	Fibers in *parallel*—bypassing direct circuit impulses to a final neuraxis level or final common path.	
3. Effector structures	Smooth muscle of midline-placed or evolved visceral organs—function of metabolism and reproduction. Behavior (movement) within the internal environment in reaction to *internal* needs.	Striated para-axial or trunkal muscles, i.e., musculoskeletal riggings of body wall (motocord induced) and striated cranial muscles (primordial cephalic end gut induced)—function of outward expression of internal environment, sensation or "feelings", i.e., emotional expression. Behavior expressed outward in reaction to internal needs.	Striated muscles of body appendages, i.e., musculoskeletal riggings of extremities, particularly of the hands and fingers—function of effective transaction with the external environment. Behavior (movement) in relation to external object, with body object as goal. (Figs. 1 and 2.)	
4. Anatomic frame of reference of 3 phylo-ontogenetic phases of behavior as evolved in the human brain.	Motility (behavior) common to all vertebrates—i.e., visceral in relation to metabolism, nutrition and reproduction—no longer in evolution.	Motility of instinctive, innate, i.e., emotional character, which behavior is not so universal or common but *species* specific—no longer in evolution.	Motility derived from individual experience, in constant evolution. Not only species specific (human) but individually specific.	
5. Neuroanatomic correlates of behavior, i.e., motility, for motility *is* behavior.	*Innermost* random or diffuse neuronal system controlling motility (behavior) of medially evolved or placed viscera (Fig. 5, *A*).	*Intermediate* nucleated neuronal cell body groupings of evolved younger portions of rhinic and older portions of limbic systems regulating inward expression of visceral motility and outward (somatic) expression through musculoskeletal riggings (Fig. 5, *B*).	*Outermost* younger evolved striate-laminate limbic and the supralimbic cerebral cortical systems creating and regulating the more strictly human behavior (motility) of effective transaction with the external environment (Fig. 5, *C*).	
6. Space orientation in relation to body sidedness (right and left)	*Absent:* Knows not (unaware of) sides of body.	*Absent* and *Present:* *Absent* with respect to extracorporeal environment. *Present* with respect to intracorporeal environment—but rt. and lt. limbic systems homonymous structures, thus functionally equipotential.	*Present:* *Present* supralimbic right and left systems structurally asymmetrical (heteronymous)—thus preferential rt. and lt. (i.e., handedness, rt. and lt. body awareness, visual dominance) with respect to both extra and intracorporeal environment.	

7. Language	Awareness of internal environment without outward expression, thus intimately *private*, ineffable (unspeakable) internal experience.	External expression of the internal state with crude sounds (cries, hisses, etc.), i.e., limited sound symbols, therefore crude language, making public (emoting) private internal experience.	External sound symbol expression (public) of internal elaborated symbolized thought (private) in reaction to effective transaction with the external environment—i.e., social communication
8. Function	Visceral motility (metabolism, nutrition, respiration and reproduction), therefore intimately *private*, unspeakable, internal experience. No reference to sidedness or laterality.	Sensory recipient and emotional expression through musculoskeletal riggings of the trunk and head—movements are bilaterally symmetrical, in response to *body* itself and not to external objects. Behavior is instinctive, therefore predictable, perennial and short-term. Response to unconditioned stimuli (physical agents)—light, sound, temperature and mechanical contact.	Motility (behavior) of effectuation, i.e., creation or manufacture. Symbolized thought (private) and language (public). Relatively emancipated from affective input of lower levels of neuraxis. Behavioral response to conditioned stimuli (memory).
Pathology of:	Diminished or excessive visceral input (sensory) and output (motor) leads to decreased or increased visceral effectuation influences on expressive (behavior, motility) functions of limbic and supralimbic systems—i.e., apathetic-withdrawal or hyperactive visceral specifically human pathologic behavior states.	Diminished or excessive input influences from (a) rhinic visceral level and (b) limbic—kinesthetic input from striate musculoskeletal structures into the supralimbic system leading to apathetic, excessive or unbalanced effectuation, including language communication with the outside world. Impairment of perception to sensory modalities, therefore to unconditioned stimuli.	The transitional limbic-supralimbic sensory projection zones when injured cause impairment of behavioral response to conditioned stimuli. Pathology to postcentral supralimbic lobe leads to disarray of symbolization of experience into language and relevant action. Pathology to precentral supralimbic system leads to inability to translate private experience into public acts of socially relevant behavior.

The effector organs for the limbic system are the bilateral, essentially symmetrical, musculoskeletal riggings of the symmetrical trunk and proximal portions of the extremities. The development of right or left preference (asymmetry) in the terminal portions of the extremities, particularly the hands and fingers, arises from a later evolvement that calls for more refined dominance and discrimination. The limbic system is the neurogenic correlator and coordinator of external expression of internal feeling. Emotional behavior is probably related more to the limbic system than to later-developing higher centers. Disorders of emotional behavior include the benign neuroses and malignant affective psychoses.

Both the rhinic and limbic systems exert a most important, dynamic influence on the development of the supralimbic system and its specifically human behavioral functions of symbolic thought, language and transaction with the external environment (persons and objects). As stated by Conel,[7] "Increase in control of the striated muscles is concomitant with increase in the development of the cerebral cortex (supralimbic system) both phylogenetically and ontogenetically." The supralimbic system, which evolves from the limbic system, regulates the elaborate use of the terminal musculoskeletal riggings of the hand and fingers and of the oral and respiratory muscles (Fig. 2). As a result, the human develops behavior for the manufacture or creation of inanimate objects and communication with animate objects. Symbolic thought of learned experience (memory) is an evolving function of the postnatal unfolding of the terminal zones of the postcentral portion of the supralimbic cortex projected from the primary cortical sensory projection areas (Fig. 4). Paralleling this is the development of behavior of transaction with the external environment (manufacture, creativity and language), a function of the terminal zones of the precentral portion of the supralimbic cortex from the primary motor projection areas (Fig. 4). This includes (a) the more elaborate use of the hand and fingers in relation to the environment (Figs. 1 and 2), and (b) the even more complex use of the oral and respiratory striate muscles for public communication; i.e., language, the basis for our complex social order (Fig. 4, *B*). These postcentral (symbolic thought) and precentral (manufacture and language) terminal zones of the supralimbic system are the ontogenetically youngest and, therefore, specifically human portions of the cerebral cortex that are nonexistent in lower primates.

The neural organization of the rhinic system is random (Fig. 5, *A*). That of the limbic system is in series; i.e., predominantly cingulus to striate to pallidum, pallidum to thalamus, thalamus to tectum to final common path of the anterior horn (Fig. 5, *B*), which is the final common effector stimulant to the musculoskeletal riggings. Animals with a well-developed rhinic and limbic system have acquired a bilateral symmetrical

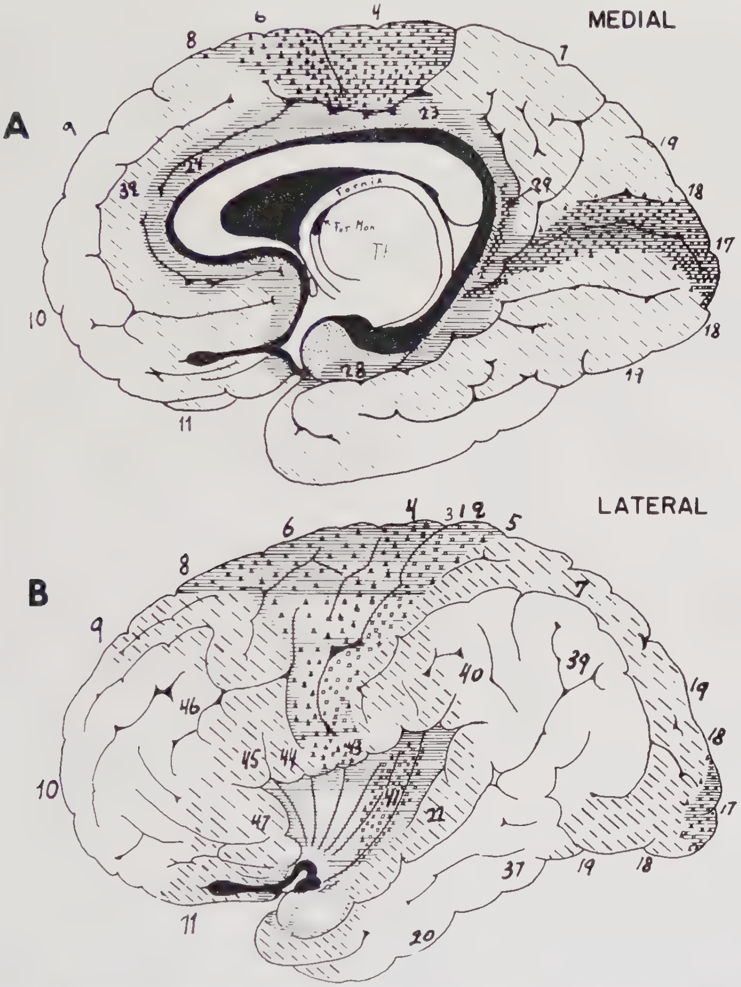
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Fig. 4. *A*, Medial view of the right cerebral hemisphere. *B*, Lateral view of the left cerebral hemisphere with the Sylvian fissure open to show the island of Reil. Solid black bordered by fine stipple: rhinic lobe; syn: allocortex (O. Fogt), paleo- and archicortex (I. Filimonov), entopallium. Horizontal lines: limbic lobe; syn: mesopallium. Horizontal lines with triangles and small circles: primary sensory and motor projection zones (limbic extensions into the supralimbic lobe). Diagonal dash-lines and areas left white: supralimbic lobe. Diagonal dash lines: paralimbic or marginal zones of the supralimbic lobe. White: terminal zones of the supralimbic lobe. (From Yakovlev, P. I.: Anatomy of the Human Brain and the Problem of Mental Retardation. *In* Bowman, P. W. and Mautner, H. V. (eds.): Mental Retardation: Proceedings of the First International Medical Conference. New York, Grune and Stratton, Inc., 1960, by permission.)

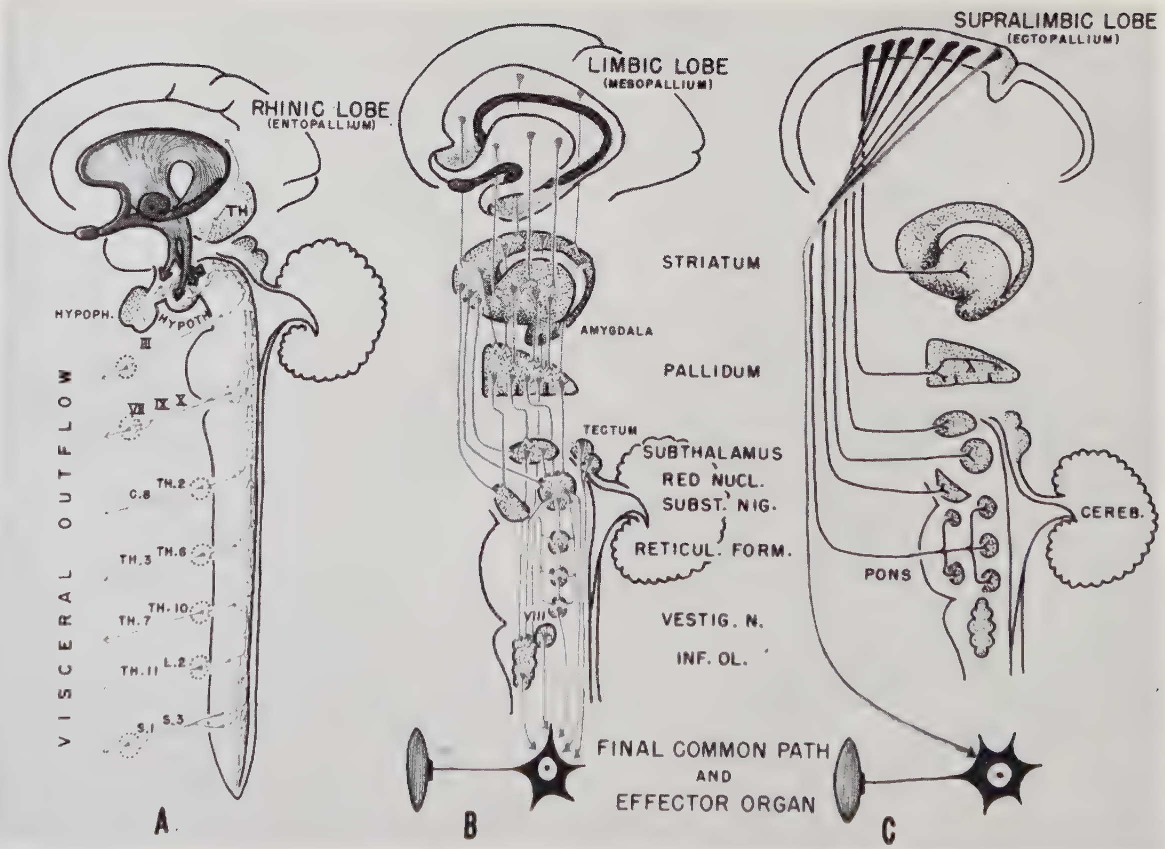
SUPRALIMBIC LOBE
(ECTOPALLIUM)
LIMBIC LOBE
(MESOPALLIUM)
RHINIC LOBE
(ENTOPALLIUM)
TH
HYPOPH.
HYPOTH.
III
VII
IX
X
C.8
TH.2
TH.3
TH.6
TH.7
TH.10
TH.11
L.2
S.1
S.3
VISCERAL OUTFLOW
STRIATUM
AMYGDALA
PALLIDUM
TECTUM
SUBTHALAMUS
RED NUCL.
SUBST. NIG.
RETICUL. FORM.
VIII
VESTIG. N.
INF. OL.
CEREB.
PONS
FINAL COMMON PATH
AND
EFFECTOR ORGAN
A
B
C

Fig. 5. Three systems of neuronal assemblies in the neuraxis. *A*, innermost system of visceration, neuronal cell bodies and axons in random arrangement. *B*, Intermediate system of expression, neuronal arrangement characterized by cell bodies in groups (nuclei) and axons in series. *C*, Outermost system of effectuation, neuronal arrangement with cell bodies in layers (laminate) and axons in parallel. (From Yakovlev, P. I.: Anatomy of the Human Brain and the Problem of Mental Retardation. *In* Bowman, P. W. and Mautner, H. V. (eds.): Mental Retardation: Proceedings of the First International Medical Conference. New York, Grune & Stratton, Inc., 1960, by permission.)

musculoskeletal effector mechanism that enables them to communicate their internal dynamic state to the external environment. They do not have the ability to transact or communicate with the environment in reaction to external objects. The supralimbic system has added to the random organization of the rhinic system and to the in-series organization of the limbic system a very effective in-parallel neural organization (Fig. 5, *C*). This permits the supralimbic system to essentially bypass the limbic and rhinic systems by a more direct route to the control of the final common path. This path is the effector system of (a) manufacture, primarily through the hands and fingers, and (b) communication through the muscles of speech and respiration.

Five features characterize the supralimbic system of the cerebral cortex in man:

1. The supralimbic cortex has retained its embryologic potentialities of maturation not only in continuing myelinization of the subcortical white substance in childhood[8, 17] but also in continuing intracortical myelinization and elaboration of dendrites extending into adult years.[24] Clinically, this is expressed during the life span of man in acquisition of new knowledge and the recognition that wisdom increases with age.

2. The brain expands three-dimensionally; i.e., anteriorly, laterally, posteriorly, and inferiorly-anteriorly; or, expressed in conventional lobes of the brain: the frontal, parietal, occipital, and temporal cerebral lobes, respectively. This expansion is illustrated in the lightly shaded and unshaded terminal zones of the precentral and postcentral cerebral cortex of Figure 4.

3. The supralimbic system of the cerebral hemispheres unfolds with increasing asymmetry of its homologous regions.[7, 25] The evolving asymmetry is greatest in the terminal regions of the supralimbic system (Figure 4). This asymmetry is the neuroanatomic basis for the awareness of right and left bodysidedness and, more important, preferential right or left handedness. It adds to man's ability to discriminate between objects in the external world and is probably the neurobiologic basis for man's ability to place opposing values on abstract concepts, including society, morals and economics. Examples of opposing values are Heaven or Hell, good or bad, healthy or unhealthy, and rich or poor. The embryologic potential of continuing individual heteromynous and preferential elaboration between the terminal regions of the right and left supralimbic systems is therefore a highly complex, specifically human function of the supralimbic system in man.[18, 26]

4. The direct in-parallel fiber connections of the supralimbic system by-pass the intermediate levels of the neuraxis on the way to the final common path[7] (Fig. 5, *C*).

5. Probably the most important feature of the supralimbic system is that its terminal zones become more emancipated from the limbic and rhinic systems, from which it initially evolves.[14, 36] The terminal zones

of the supralimbic system are not so intimately thalamus-bound as the preterminal ontogenetic older portions of this system.[36]

Thus, from the relatively emancipated terminal (specifically human) portions of the supralimbic system with its multiple intra- and intercortical synaptic time-consuming correlations between the sensory input (affective) and motor output (effector-common path), there evolves the specifically human CNS function of judgment and reason.[14] Here also is found the correlation between stored memories and perceived exteroceptive sensory inputs, which is never without the background coloring of the visceral affective input through the thalamic, transitional limbic-supralimbic systems.

It is not possible in this essay to cover all the clinical categories of behavioral disorders. To illustrate the clinical usefulness of this ontogenetic neuroanatomic frame of reference, two symptomatic types of behavior disorder will be discussed: (1) mental subnormality (mental retardation) and (2) disorder of human emotion.

MENTAL SUBNORMALITY AND THE CONCEPT OF ONTOGENESIS OF THE BRAIN

One of the major problems of neurology today is mental retardation, not only profound retardation but also less obvious, though equally important, borderline or less than average intellectual impairment.[22] "Mental retardation" as used in this essay is defined as impaired behavior development resulting from damage to the central nervous system before it has reached its major degree of teen-age or adult maturation. Mental retardation, whatever the etiology, occurs in the great majority of instances before the brain has reached the maturation of later childhood. Thus, the foregoing ontogenetically oriented rhinic, limbic, supralimbic frame of reference becomes an important tool in the diagnosis, prognosis or treatment of mental subnormality.

Considerable ignorance still exists concerning the etiology of mental subnormality. Etiologic discoveries are potentially present in the current genetic-chromosome studies, Rh factors and neurochemic, including enzyme system, investigations. Specific etiologic progress has been made in certain instances; for example, excessive phenylpyruvic acid accumulation in the blood leading to mental retardation. In spite of these promising fields of study, the specific cause for the great majority of cases of mental retardation remains unknown, and the pediatrician or family physician is faced with making a diagnosis at a descriptive level. Not being able to make a specific etiologic diagnosis, the physician may be able, by orienting the CNS deficit and related impaired or defective behavior to the ontogenetic frame of reference, to make a diagnosis based on pathogenesis and to relate it to time of onset; i.e., to prenatal, natal or postnatal periods of the life cycle. Often he will be able to make a diagnosis on the basis of ontogenesis, which will aid him in making a more intelligent prognosis that would include self-support and social adjustment. This will aid in programming future training in a special school or state hospital.

The following general principles that are oriented to the ontogenetic frame of reference are given as guides for the evaluation of mental subnormality or retardation:

1. Mental subnormality or retardation usually occurs before the brain has reached its teen-age ontogenetic level of maturation.

2. In general, and other factors being equal, the earlier the brain is injured in its ontogenetic maturation, the more severe the behavioral impairment.

3. The earlier the injury to the CNS, the greater the *apparent* or *actual impairment* of behavior retardation .in comparison with the chronologic age of the individual. For example, an infant who acquires permanent damage to his rhinic,* limbic and supralimbic systems from a viral encephalitis at one month of age may initially show only limbic and transitional limbic to supralimbic pyramidal and extrapyramidal signs. This is not because of continuing viral damage to the ontogenetically younger portions of the limbic and supralimbic systems, but because these levels failed to mature as a result of the acute encephalitis at one month of age. The initial, acute stage of the viral encephalitis impairs the postnatal embryologic developmental potentialities of the supralimbic system and thus slows ontogenetic evolvement. Since the supralimbic system is not clinically functioning at one month of age, damage to this system cannot be measured until it has matured to the stage of influencing psychologically measurable behavior. The gap between impairment of supralimbic maturation and age continues to widen as chronologic age increases.

4. When the ontogenetic terminal portions of the supralimbic system are damaged before they have matured to the point of initiating more complex motor and specifically human manufacture, creative and language behavior, *without* damage to the rhinic and limbic systems and ontogenetically older portions of the supralimbic system, clinical sequelae will be *delayed* and not appear until months or years later. Such initial injury occurs during the late prenatal or natal period, in infancy, or during the early childhood years.

Two case reports will illustrate the clinical manifestations of early injury by viral encephalitis. In the first report, the patients (twins) initially showed limbic and transitional limbic to supralimbic signs with later progressive regression that indicated damage to the maturation potentialities of the supralimbic system. The second report describes a child without damage to the rhinic and limbic systems, who later showed evidence of damage only to the supralimbic system.

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* An infant cannot survive severe damage to the rhinic system because neural integration of visceral and metabolic functions is essential for life.

CASE I. Fraternal twin girls became ill at 5 days of age. Both were acutely ill with high fever, repeated convulsions, lethargy, neck rigidity, dehydration and bulging fontanels. A diagnosis of Western encephalitis was established by viral laboratory studies, and the mode of infection was through transplacental transmission of the virus a few days before birth. Both children showed early neurologic evidence of motor impairment with spasticity and retardation in crude infant behavior. They became restless and continued to have intermittent convulsions. By the age of 7 years, the child who had always shown the greater degree of impairment could no longer walk, had no speech, and had not developed self-care skills. The other child was functioning at the 3-year level of locomotion and scored below the 1-year level in communication.

The regression of behavior maturation in these twins was not the result of progressive destruction of cerebral parenchyma by the virus; rather, it was due to the failure of the immature neonatal brain, damaged before one month of age by the acute viral encephalitis, to mature at a normal pace.

CASE II. An apparently normal 28-day-old male infant became acutely ill with fever, convulsions, drowsiness, tremors, twitches and restlessness. A diagnosis of Western encephalitis was established by viral laboratory tests. The infant made a good clinical recovery. During the first 2 years, neurologic examinations revealed no abnormalities, and the child was described as having average mental capacity, good social responses, and appropriate physical and behavioral development for his chronologic age. By the age of 3, his parents expressed some concern about his delay in developing speech. This delay has persisted and the gap between expected and actual performance has widened as he has grown older. At the age of 9 years and 10 months, his IQ was 83. He had poor speech, difficulty in organizing his thoughts to express answers clearly and adequately, and had perceptual difficulties. Although his gross motor ability was normal for his age, his fine motor coordination was impaired.

These delayed sequelae indicate impairment of ontogenetic maturation of the supralimbic system, particularly the terminal zones.

EMOTIONAL DISORDERS AND BRAIN DYSFUNCTION

Emotional expression is one of the major segments of human behavior. It has been stated that 60 per cent of medical problems fall in the emotional realm. Emotional disorders include the benign neuroses, anxiety states, hysterias and the more malignant reactive depressions, involutional melancholias, manic-depressive and schizo-affective disorders. For the diagnosis, treatment or prevention of emotional disorders, a physiologic anatomic understanding of emotional behavior is essential. Neurobiologically, emotion is an expression of an internal (private) state by internal smooth (private) and surface striate (public) muscle motility.

Emotion includes: (1) internal private experience, primarily from the visceral and proprioceptive sensory input to the postcentral perceptual and comprehension zones of the terminal portions of the supralimbic system; and (2) the correlation of the postcentral with the precentral effector terminal zones of the supralimbic system for outward (public) expression of internal needs. This expression is accomplished through the striate extremity, facial, respiratory and oral muscle behavior, but *input*-regulated at all three levels—the rhinic, limbic and supralimbic. A specific elaboration of human emotion is that effected at the supralimbic level by the more complex expression of the internal state through language communication. In other words, emotion is movement from inner feelings to outer expression.

To repeat this, "emoted" behavior results from two main sources: (1) the visceral kinesthetic receptors of smooth muscle, and (2) kinesthetic receptors of the muscles, tendons and joints of the striated musculoskeletal riggings. Sensory input, in particular visceral and musculoskeletal kinesthetic sense, is essential to awakeness, alertness, attentiveness and concentration via the brain stem reticulo-thalamic intralaminar-diffuse cortical activating system. The intralaminar nuclei of the thalamus play a nonfocal, diffuse alerting influence on the limbic and supralimbic systems of the cerebral cortex. Emotional awareness (private) and the resulting emotional behavior (public) are primarily the result of the quantitative increase above or decrease below the neutral or average level of sensory input, particularly visceral and musculoskeletal kinesthetic sensation shunted into the brain stem reticular and thalamic intralaminar neurons to the supralimbic cortex.

The CNS is not a sensory organ, even though it receives visceral and somatic sensory stimuli from the sensory receptive organs; therefore, the CNS is incapable of sensory awareness without sensory input. It follows that emotional feelings are nonexistent without input from the visceral and somatic, particularly kinesthetic, sensory receptors. Afferent emotional awareness (private) is not possible without sensory input. Therefore, the CNS has as one of its major functions the correlation of sensory input, including visceral and kinesthetic sensation, in the regulation of nerve impulse output to the common final path for the expression of emotional behavior through the effector smooth and striate muscle organs. This neuroanatomic and physiologic knowledge is of fundamental importance in the scientific approach to the prevention and treatment of unhealthy emotional states and their by-products.

The most important and clinically seldom appreciated by-product of unhealthy, depressed or excessive kinesthetic sensory input is influence on thought symbols (private) and resulting communication behavior – language (public). The saying "One believes and thinks as one feels" has its clinical support in the previous sentence. The constitutionally emotionally labile, unstable, underactive, depressed or overactive excitable (emoting) person's colored or prejudiced thoughts will be paralleled by his internal state of sensory (private) input (a) into the limbic-supralimbic afferent thalamic and cerebral cortical primary sensory projection zones, and (b) by way of afferent input from the brain stem reticular and thalamic intralaminar-encephalic activating system. These *a* and *b* sensory inputs into the primary postcentral sensory projection zones of the cerebral cortex are then passed on into the specifically human cortical postcentral terminal zones of the supralimbic system. As pointed out by Yakovlev,[36] "The 'visceral' or 'inner' self becomes conscient experience." The decreased or excessive sensory input modifies not only perceptual and learned conditioned experience but, more important, it also modifies the symbolization of perceptual conditioned experience into experience. Through the rich intercortical fiber connections between the postcentral symbolization terminal zones and the precentral effectuation terminal zones of the supralimbic cortical system (Fig. 4) there results a modification of language and overt action. The correlation and coordination between these postcentral and precentral terminal zones of the supralimbic system result in eventual unhealthy overt behavior, including language, effected through the final common path.

Thus, to attempt to treat personality disorders in which abnormal emotional behavior (a function of the rhinic-limbic system) is the main pathologic sign, by concentrating on modifying the patient's language content (a secondary by-product of supralimbic dysfunction) through interview therapy will at best result only in replacing one emotionally conditioned distorted language-expressed thought by another equally emotionally conditioned distorted thought because the underlying, unhealthy, emoting neurophysiology at the rhinic-limbic level persists. Individuals with more than the average degree of emotional reaction to the everyday run of environmental stress will project the cause of their privately experienced excessive emotional state onto some past, present or future potential external environmental situation or internal somatic (hypochondriacal) complaint, as symbolically consciously felt and expressed through the terminal zones of the supralimbic system. To treat an agitated depressive patient who believes that her neighbors are not being friendly to her by recommending to the patient and her husband that her agitated depressive state would be dissolved by moving to a new neighborhood would only result in the patient's soon reacting the same way toward her new neighbors, or in the transferring of this belief from the neighbors to some other person, as for example, her husband. As long as there is a continuation of an unhealthy degree of visceral and somatic (particularly kinesthetic) sensory input by way of the rhinic and limbic systems into the supralimbic terminal zones for symbolic thought and language communication, any therapeutic effort toward treatment of thought and language content at the supralimbic level will fail to bring about satisfactory improvement or recovery in a basically emotionally disturbed person. This is supported by the much more successful results through the use of muscle relaxation therapy,[12, 16] tranquilizing drugs and electric shock therapies. If the unhealthy emotional visceral and kinesthetic sensory input resulting from increased visceral and striate muscle tone is not too firmly conditioned or intense, as in the neurotic, mild anxiety states or more benign agitated depressions, the volitional muscle relaxation program, together with the judicious temporary use of tranquilizing drugs, will relieve the excessive visceral rhinic and kinesthetic limbic sensory input, the basic cause of the prejudiced or colored thought and language and related overt behavior expressed through terminal zone levels of the supralimbic system. In the more malignant types of emotional disorders (agitated depression, manic-depressive and involutional melancholias), the above conservative approach through volitional efforts by the patient will fail because the conditioning of the unhealthy muscle tone disorder at the visceral muscle rhinic and striate muscle limbic levels is too firmly patterned. Volitional conscious and willful effector efforts from the level of the ontogenetic younger supralimbic system are unable to re-educate the more fixed synaptic patterns of the ontogenetic older and lower level systems. Thus, it becomes necessary to resort to electric shock therapy with or without the combination of the more intense use of tranquilizing drugs. The working hypothesis is that this more drastic approach is able to break down the more firmly fixed synaptic patterns at the rhinic and limbic levels, which volitional muscle relaxation efforts at the supralimbic level are unable to modify. Once the excessive increased muscle tone behavior is corrected, the secondary distorted thought content and related language and behavior subside. As the patient is usually no longer preoccupied by or even interested in his previously unhealthy emotionally oriented and prejudiced thoughts and related overt distorted behavior, further interviews concerned with these previous distorted thoughts become of limited value. However, occasional follow-up interviews will help the patient keep under control his endowed tendency for excessive emoting, through visceral and striate muscle tone, in reaction to everyday (often minor) stresses of living. This is probably the most satisfactory type of follow-up interview, for if the patient is successful in preventing a recurrence of smooth and striate muscle kinesthetic sensory input, the resulting secondary thought distortion, related disturbed language and overt behavior will not recur. It is recognized that even this may not be successful, for the more malignant agitated depressive, manic-depressive disorders have a way of recurring despite the volitional efforts on the part of the patient. Follow-up tranquilizing medication or occasional follow-up electric shock therapy may be successful in some but not all of the more resistant cases. Here again, psychiatric interviews based on recurrence of thought disorders secondary to excessive emotional behavior will again fail. The use of volitional relaxation therapy and tranquilizing drugs with or without electric shock treatments results in a lower percentage of recurrence of what is probably a genetically endowed emotional disorder. In the more resistant cases, one is probably dealing with some recurrent inborn genetically determined pathoneurophysiologic or neurochemical-hormonal mechanism whose influence continues primarily at the level of the rhinic and limbic systems.

SUMMARY

A neuroanatomic, phylo-ontogenetically oriented frame of reference is presented for the better understanding of human behavior and for a guide in treating behavior disorders. This frame of reference consists of the rhinic, limbic and supralimbic systems of the human neuraxis, as defined and elaborated by Yakovlev. Through the use of this concept, human behavior can be correlated in time and in space with the three-dimensionally unfolding human neuraxis. It allows for the application of the many decades of accumulating basic science and clinical neurologic facts and observations to the understanding of human behavior. Using the rhinic, limbic and supralimbic human neuraxis as a framework, human behavior may be defined as the correlation and coordination of the neuraxis elements; i.e., the neurons, as expressed or effected in all spheres of motility (muscle behavior). All phases of ontogenetic human neuraxis evolution (prenatal, natal and postnatal), with their ever-evolving influences on the organ of motility—*muscle*—are included in this frame of reference.

Behavioral dysfunction may be defined as abnormal or unhealthy behavior resulting from the curtailment of the correlation and coordination of neurons. Curtailment is used in a broad or multiple etiologic sense. The curtailment may be due to genetic, acquired prenatal, natal or postnatal physical-chemical agents on sensory input from the internal and external body environment. Genetic and physical-chemical causes may curtail one or all of the rhinic, limbic and supralimbic systems. Acquired sensory input experiences will curtail or modify mainly the supralimbic system, particularly its terminal portions. As pointed out by Yakovlev, only the terminal, specifically human, portions of the supralimbic systems retain the embryologic, structurally evolving, and modifiable potentialities throughout adult years. Human individuality is the product of neurobiologic endowment and input from the physical and social environment.

The use of this conceptual framework to understand and treat behavioral disorders is illustrated by a discussion of mental subnormality and unhealthy emotional states.

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